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INDEX NUMBER

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AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
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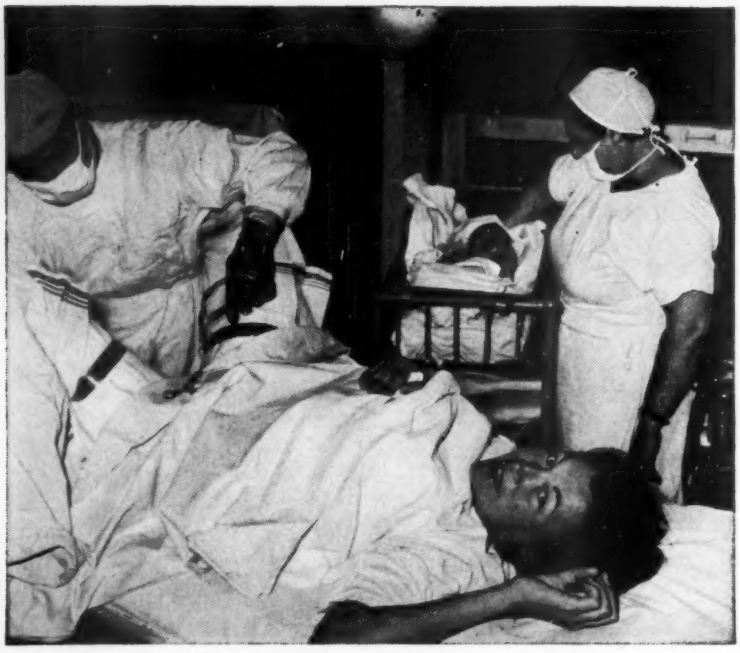

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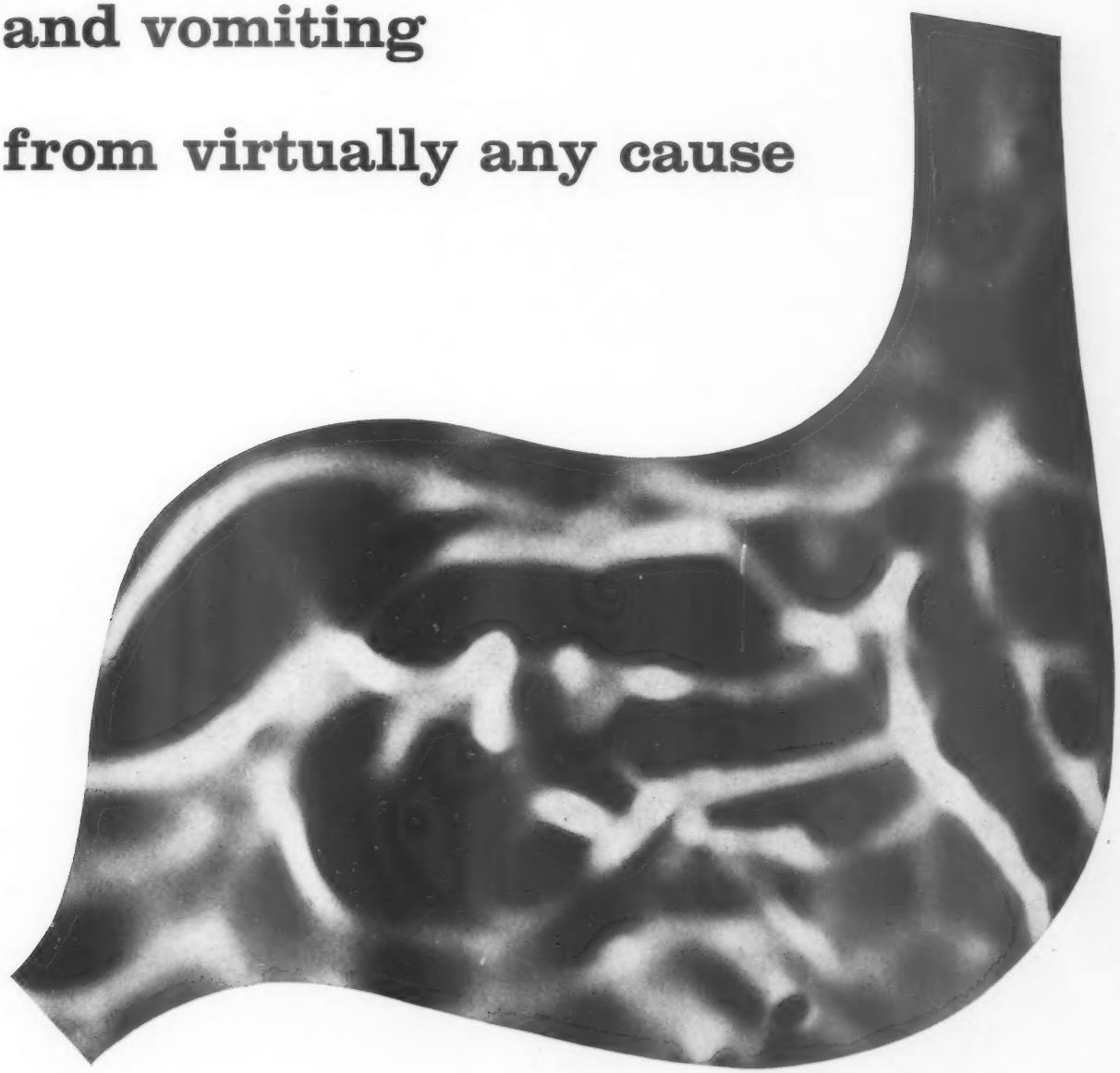

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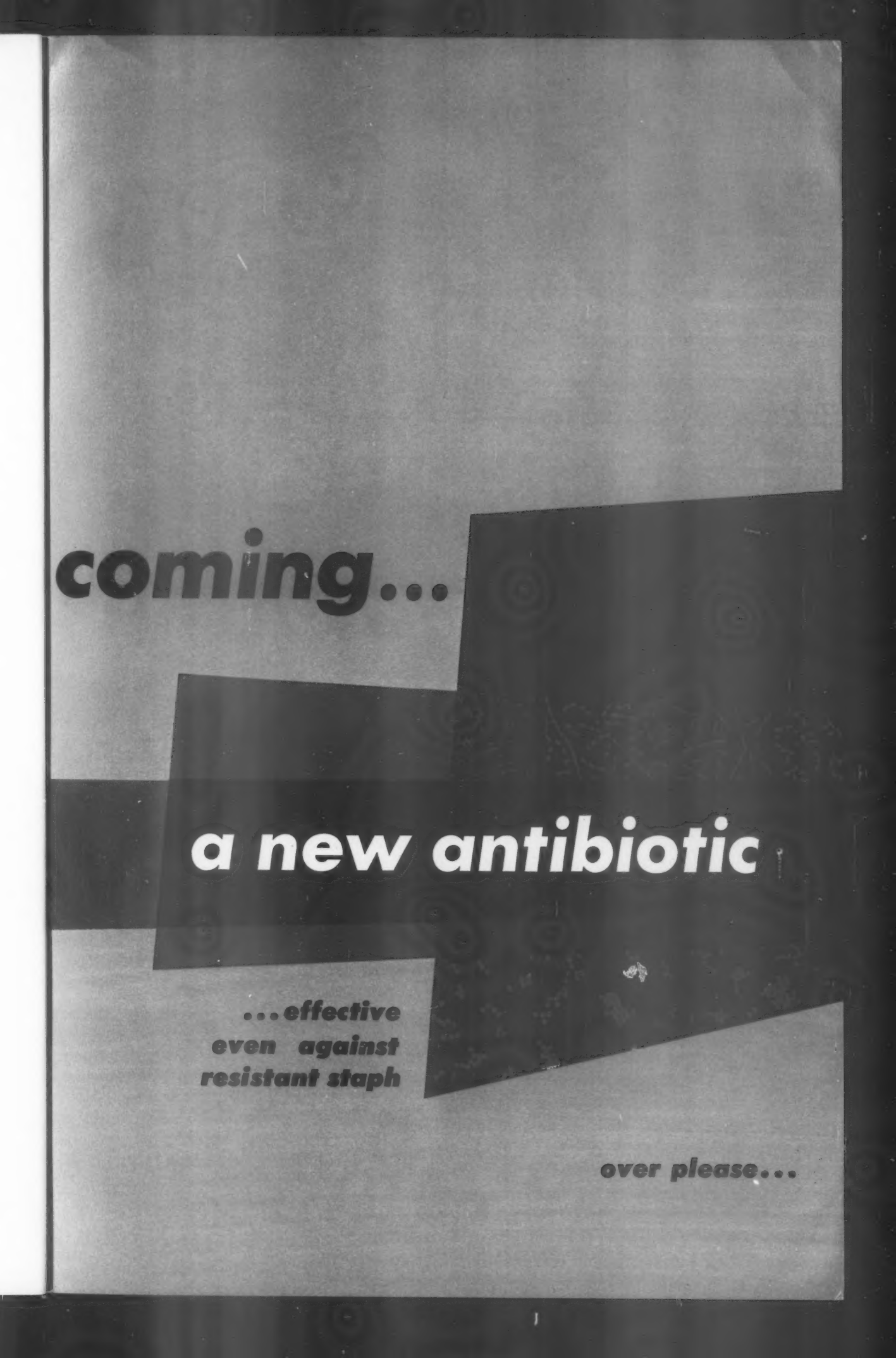
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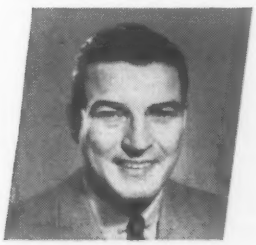

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1. Arner, O., and Others: Nord. med. *58*:1346 (Sept. 12) 1957.
2. Wilner, S.: Canad. M. A. J. *77*:199 (Aug. 1) 1957.
3. Bruner, J. M. R.: U. S. Armed Forces M. J. *6*:489 (April) 1955.
4. Diamant, A. H.: Nord. med. *48*:1324 (Sept. 26) 1952.
5. Wendt, G. R., and Cameron, J. S.: Personal communication, Jan. 4, 1955.
6. Stough, A. R.: Personal communication, Aug. 10, 1957.

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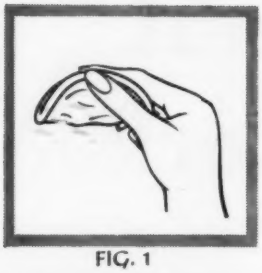

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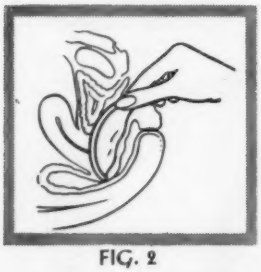

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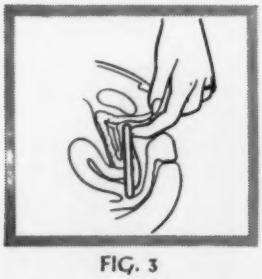

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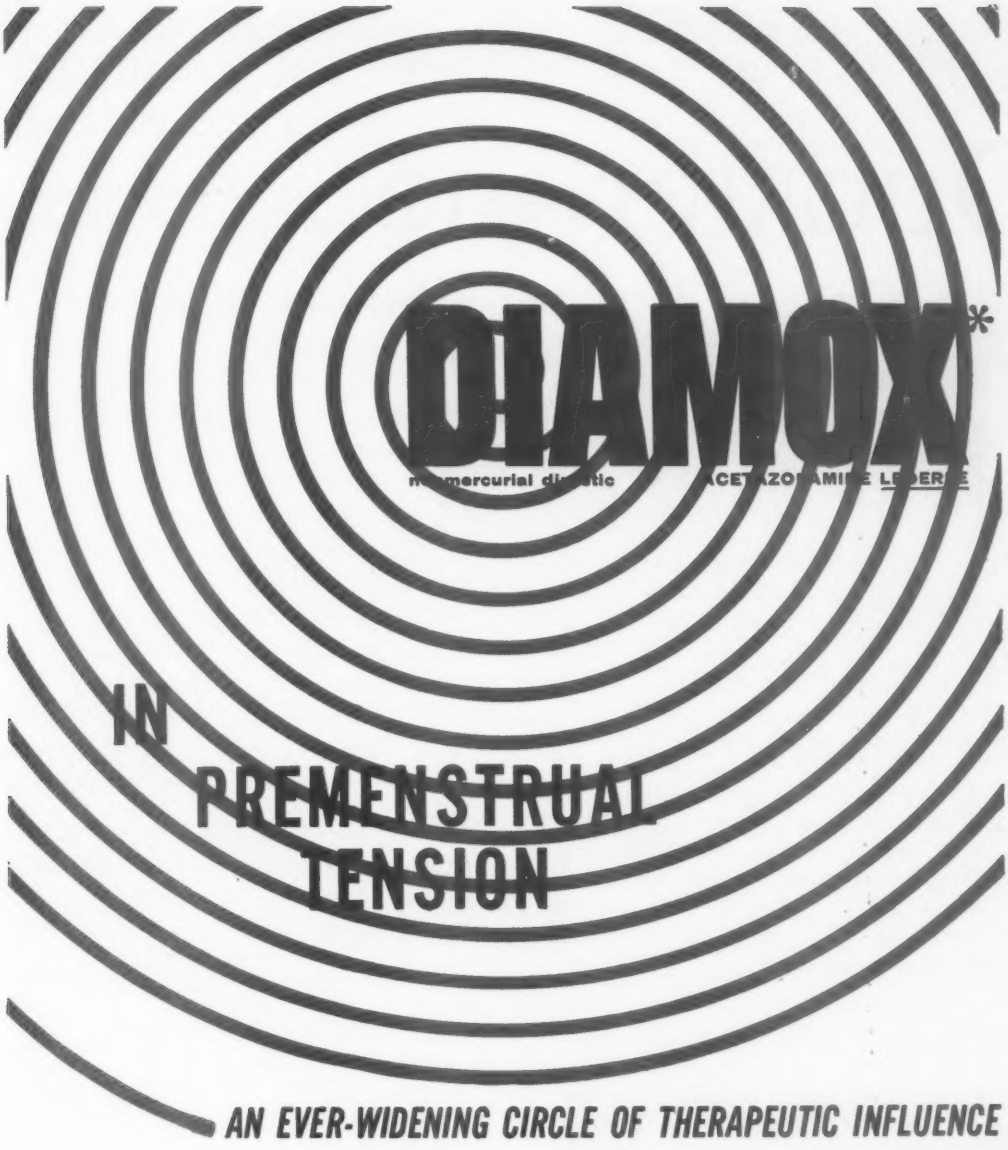

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1. Amer. J. Obst. & Gynec., 68:1321, 1954.

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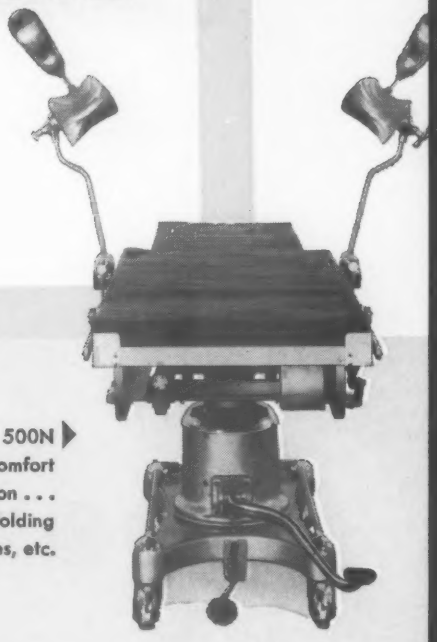

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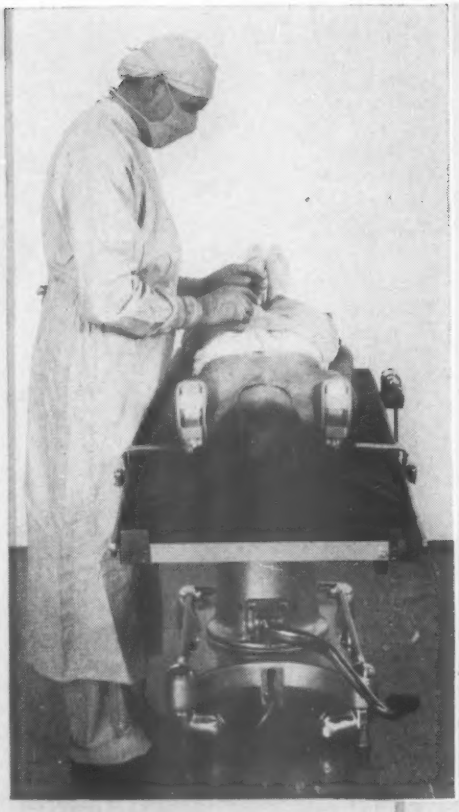

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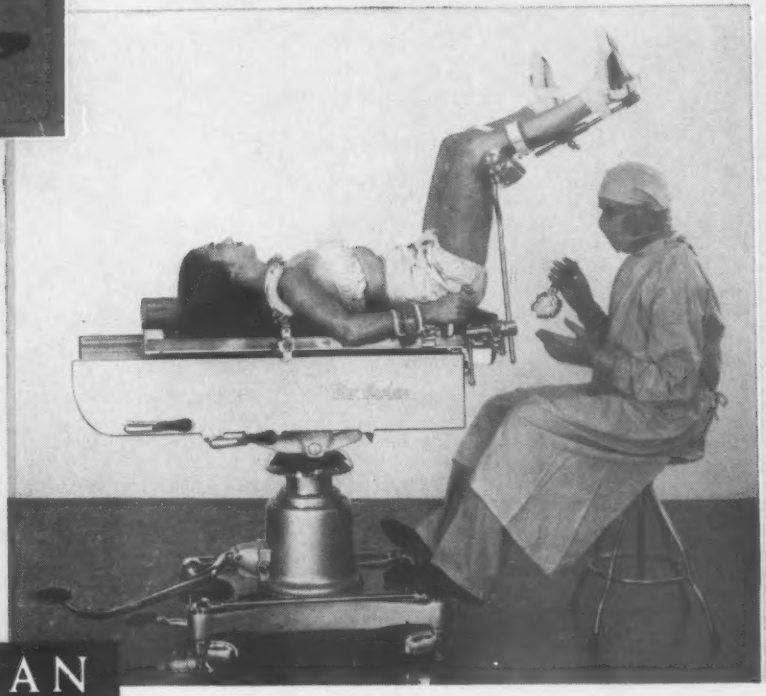

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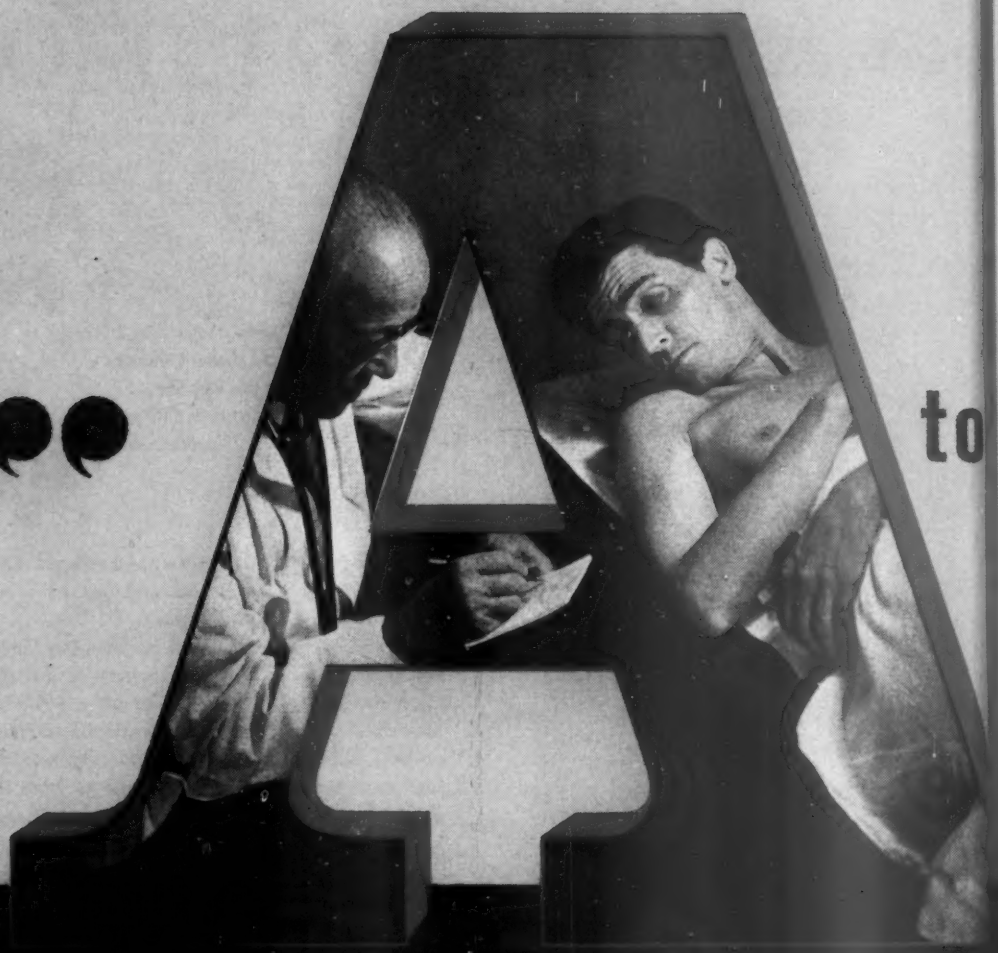


to

control ri

AZO

AZOTREX is the only urinary anti-infective agent combining —

In a single Capsule:

TETREX (tetracycline phosphate complex) 125 mg.
(tetracycline HCl activity)

Sulfamethizole ..... 250 mg.

Phenylazo-diamino-pyridine HCl ..... 50 mg.

In a 5-ml. teaspoonful of Syrup:

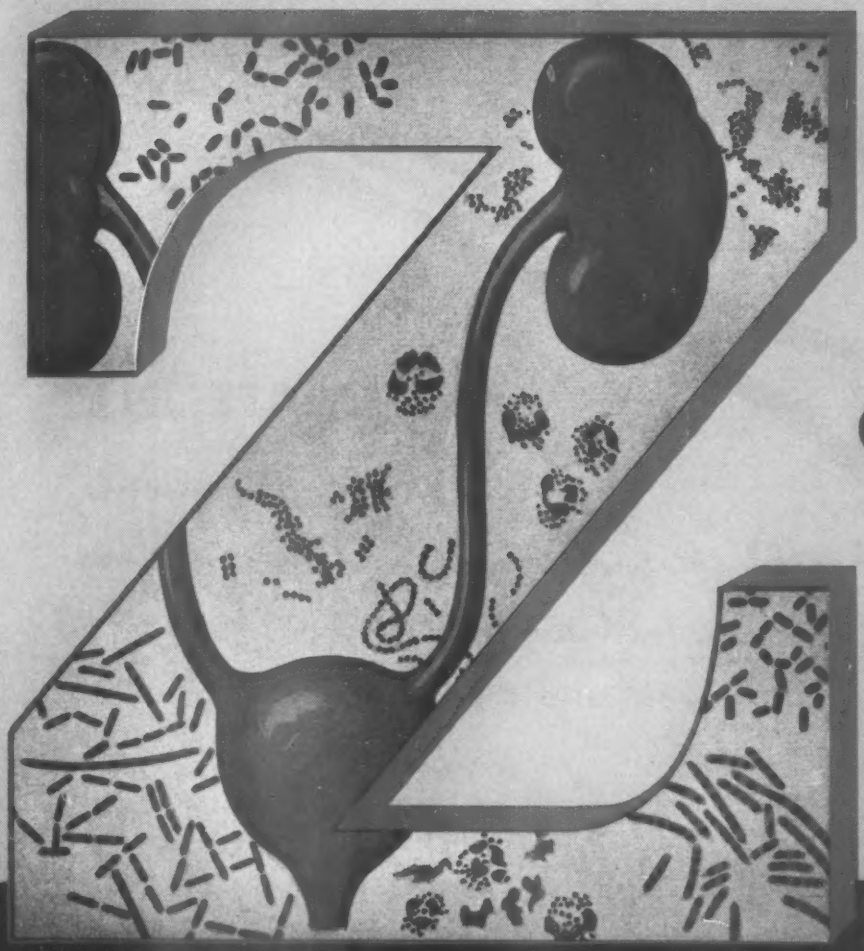
Tetracycline ..... 125 mg.
(tetracycline HCl activity)

Sulfamethizole ..... 250 mg.

Minimal adult dosage: 1 cap. or 1 tsp. q.i.d.

BRISTOL LABORATORIES INC.
Syracuse, New York

micalgesic action for



to

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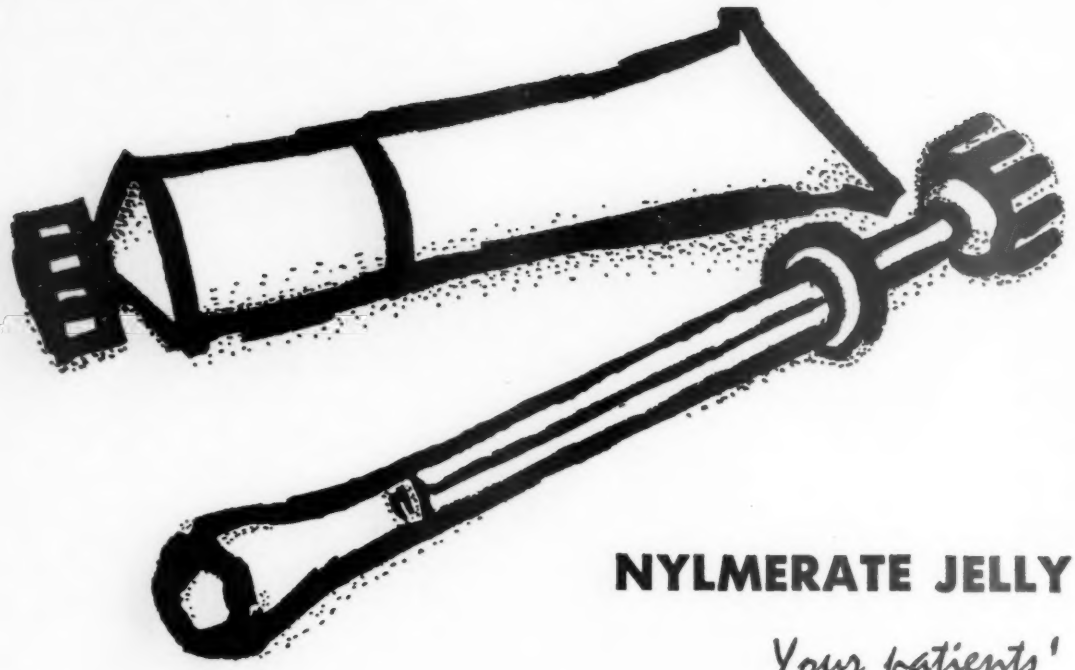
l urinary tract infections

zotrex

CAPSULES and SYRUP



NYLMERATE JELLY

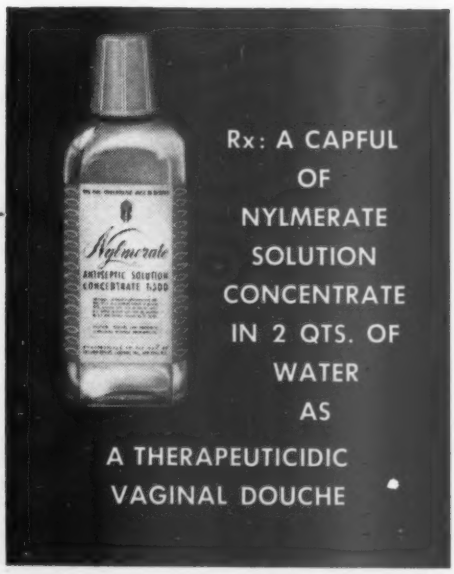
Your patients'

Vaginal discharges are problems of control and elimination with effective medication . . . in the shortest possible time! More and more physicians solve these problems by relying on . . . prescribing . . . Nylmerate, the proven therapy.*

AS A CONCOMITANT MEASURE

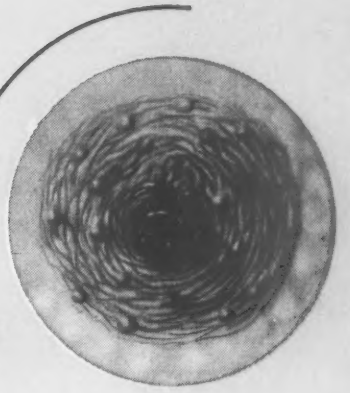
AND IN PROPHYLAXIS

USE



* Nylmerate
(brand of phenylmercuric acetate)
is effective as a trichomonicide,
monilicide and bactericide.

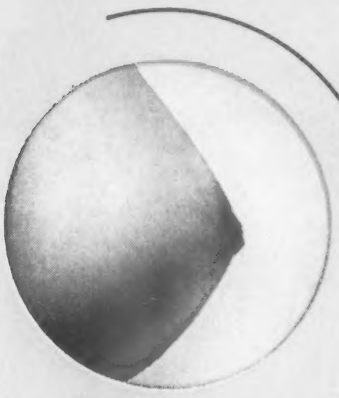
HOLLAND-RANTOS COMPANY
145 HUDSON STREET, NEW YORK 13, N. Y.



FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.

WHITE'S VITAMIN A & D OINTMENT

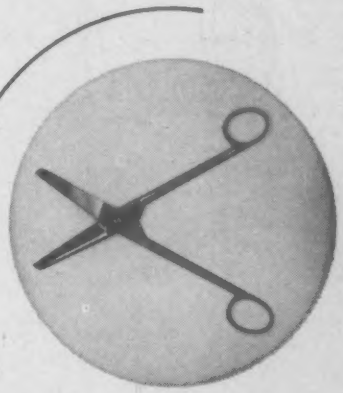


NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

AFTER EPISIOTOMIES

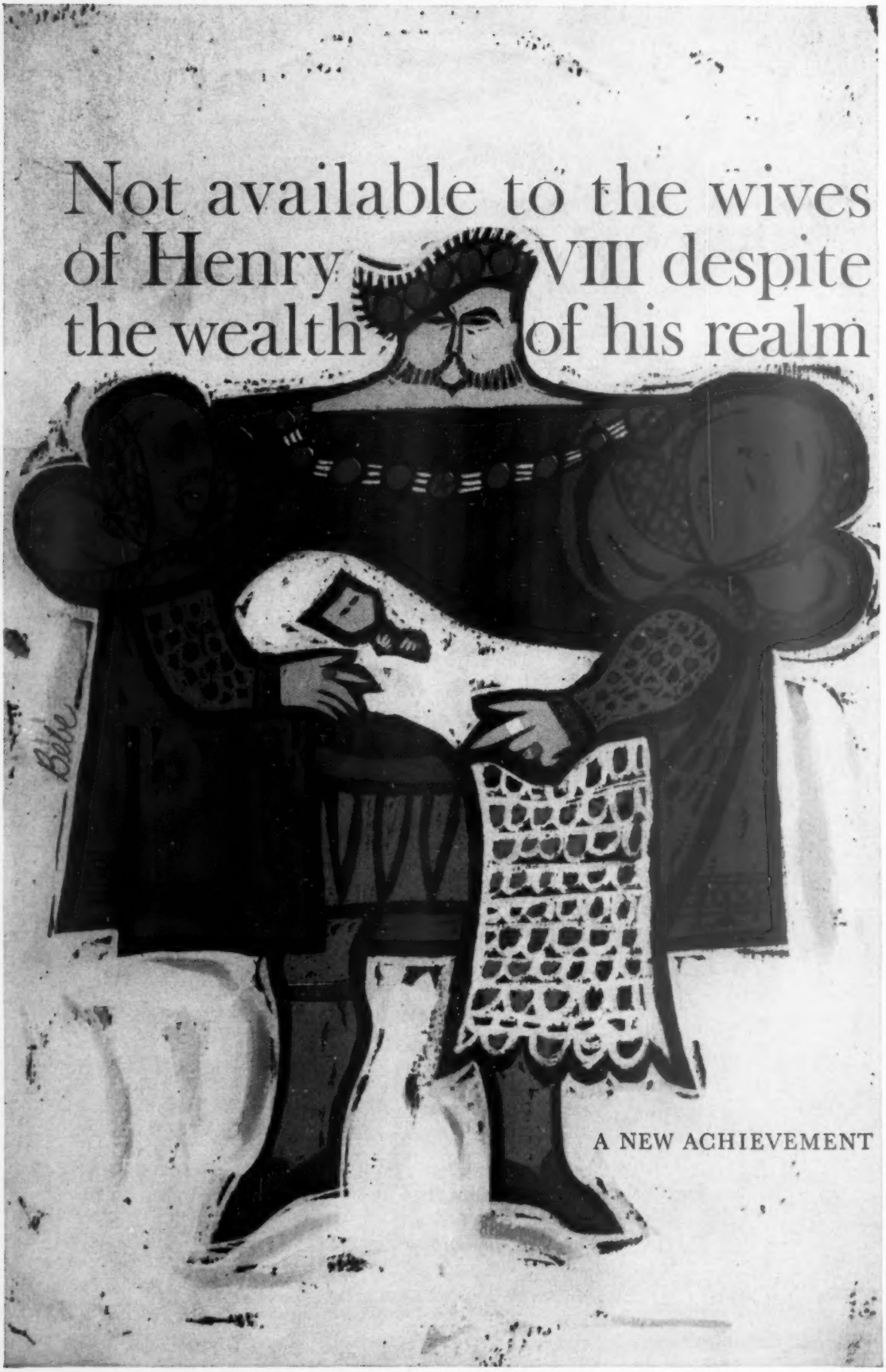
As a post-surgical dressing, White's Vitamin A & D Ointment provides comfort for the patient and encourages rapid healing.



Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers. Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.

White's

WHITE LABORATORIES, INC./KENILWORTH, NEW JERSEY


Not available to the wives
of Henry VIII despite
the wealth of his realm
A NEW ACHIEVEMENT

Now available at low cost to all your patients during pregnancy & lactation New MOL-IRON® PRENATAL

wide-range "Vita-mineral" supplement/phosphorus-free

NEW ECONOMY: less than ½ the usual cost.

NEW CONVENIENCE: only 1 tablet a day.

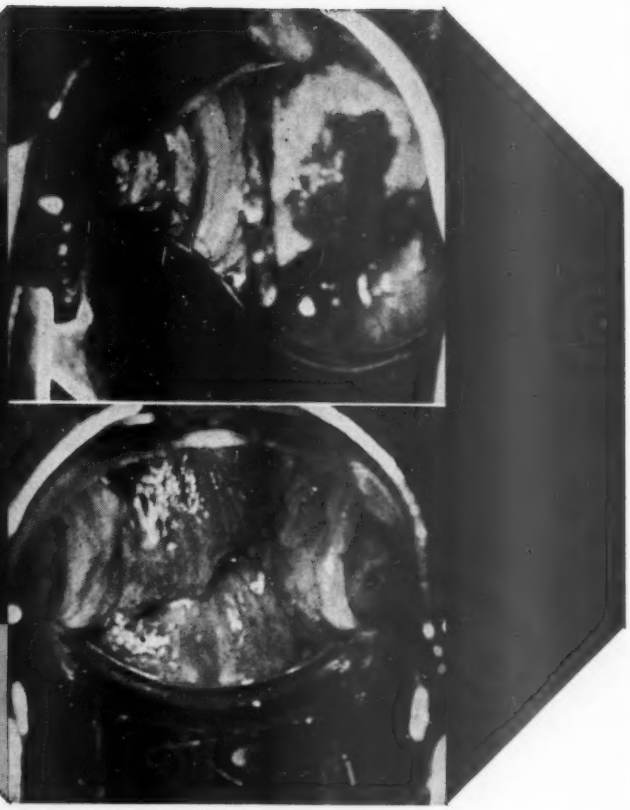
Especially "special" because of MOL-IRON, the unique molybdenized ferrous iron complex–for over 10 years unexcelled in tolerance and effectiveness, particularly in pregnant women!

Bottles of 30 (month's supply)/Bottles of 90 (trimester's supply)

White's WHITE LABORATORIES, INC., Kenilworth, New Jersey

Just one Tablet a day provides:	
Vitamin A	6000 U.S.P.U.
Vitamin D	600 U.S.P.U.
Vitamin K	2 mg.
Vitamin E	1 Int.U.
Vitamin C (Ascorbic Acid)	100 mg.
Thiamine	5 mg.
Vitamin B_{12}	2 mcg.
Folic Acid	0.25 mg.
Riboflavin	5 mg.
Pyridoxine	2 mg.
Panthenol	5 mg.
Nicotinamide	30 mg.
Mol-Iron:	
Ferrous Sulfate	75 mg.
Molybdenum Oxide	1.1 mg.
Calcium	150 mg.
Cobalt	0.1 mg.
Copper	1 mg.
Iodine	0.2 mg.
Magnesium	6 mg.
Manganese	1 mg.
Potassium	5 mg.
Zinc	1.5 mg.

WHEN YOU
WANT EXCELLENT
RESULTS IN
MONILIAL
VAGINITIS



MYCOSTATIN
VAGINAL TABLETS

Squibb Nystatin

RESULTS:
"Of 96 patients with records suitable for tabulation, 85 had from good to excellent results."[1] In a group of 13 pregnant and 12 nonpregnant clinic patients "all patients were rapidly relieved of their symptoms, within 24 hours in most cases. . . . The writer has seldom been so rapidly convinced of the value of a new therapeutic agent."[2]

Mycostatin is the safe, highly effective antifungal antibiotic . . . with direct, specific action against monilia. When you use Mycostatin Vaginal Tablets for your patients with monilial vaginitis, your therapy can be 98.3% successful.[3] And your treatment will be clean—*without messiness or staining*—a point your patients will appreciate.

Each tablet contains 100,000 units of Mycostatin and 0.95 Gm. lactose. Packages of 15 with applicator; packages of 100 without applicator. Each tablet individually foil wrapped.

Therapy: 1 tablet intravaginally once to twice daily for 2 weeks, or as required.

You can also use Mycostatin Oral Tablets; Mycostatin Ointment; Mycostatin Dusting Powder; Mycostatin for Suspension.

1. Thomas, H. H.: Obstet. & Gynec. 9:163, 1957. 2. Browne, A. D. H.: J. Irish M.A. 40:86, 1957. 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268, 1956.

"MYCOSTATIN" IS A SQUIBB TRADEMARK

SQUIBB

SQUIBB QUALITY—
THE PRICELESS
INGREDIENT

A brighter "Good morning, doctor!"

No complaints about

* post-episiotomy,
* tender hemorrhoids,
* or fissured nipples when you prescribe

Americaine® Topical Anesthetic

Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

What about sensitivities? None reported in over 11,800 published clinical cases[1]...negligible incidence in 10 years' steadily growing use.

Americaine Aerosol

For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

Americaine Ointment

For simple manual application. Available in 1 oz. tube w/applicator.

1. References on request.

ARNAR-STONE LABORATORIES, INC., *Mount Prospect, Ill.*

NOTICE TO SURGEONS

The Surgical Products Division, American Cyanamid Company, takes pleasure in announcing a new development of outstanding importance to your hospital...and to your patients.

In the past we have worked with surgeons and hospital personnel to introduce such important product advances as the new all-purpose D & G Elliptron* Surgical Needle, the revolutionary D & G Surgilar® and D & G Surgilope SP* plastic suture packages that give you safer, stronger, more flexible sutures, and a complete line of Vim hypodermic syringes and needles.

Now, in a sweeping move to provide hospitals with faster, more efficient service and reduce hospital costs substantially, Surgical Products Division introduces a plan by which hospitals may purchase all products directly from the manufacturer!

Key personnel responsible for purchasing in your hospital are now being given full details on the DIRECT-PURCHASE PLAN. This exclusive innovation will save the average hospital thousands of dollars a year on quantity purchases...and at the same time give them the added benefit of more efficient service and new rapid delivery provided by our large staff of highly trained representatives and our unparalleled network of branch offices and regional supply centers.

The DIRECT-PURCHASE PLAN is bound to become an important topic of discussion among your hospital associates. We think you'll agree that it marks one more important step in our comprehensive program to bring your hospital the finest products at the lowest possible cost.

NEW MONEY-SAVING DIRECT PURCHASE PLAN FOR HOSPITALS

CYANAMID
AMERICAN CYANAMID COMPANY
SURGICAL PRODUCTS DIVISION
NEW YORK, N. Y.

SALES OFFICE: DANBURY, CONN.

PRODUCERS OF DAVIS & GECK BRAND SUTURES AND VIM® BRAND HYPODERMIC SYRINGES AND NEEDLES.
DISTRIBUTED IN CANADA BY: CYANAMID OF CANADA LIMITED, MONTREAL 16, P.Q. *Trademark

But surely...

the lady will be dainty

- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder is buffered to *maintain* an acid condition in the vaginal mucosa. It is more effective than vinegar and simple acid douches.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill® powder

when recommending a vaginal douche

INDICATIONS:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

Currently, mailings will be forwarded only at your request.
Write for samples and literature.

The S. E. MASSENGILL Company

BRISTOL, TENNESSEE
NEW YORK SAN FRANCISCO KANSAS CITY

In modern feminine hygiene

and therapy

massengill powder

Massengill Powder has cosmetic elegance. Its clean, refreshing fragrance is acceptable to the most fastidious for therapeutic or routine hygienic use. Massengill Powder solutions are easily prepared, convenient to use, nonstaining. They effectively cleanse, deodorize and soothe the vaginal mucosa, while their mild astringent properties tend to decrease vaginal secretions.

CLEAN-UP AFTER ANTIBIOTICS

Following intensive antibiotic therapy, increasing numbers of female patients return complaining of vulvar pruritus or vaginitis . . . and profuse vaginal discharge.

Most of these present the classical picture of Monilia albicans, Trichomonas vaginalis or mixed infections. When these infections occur, regular use of Massengill Powder, with its pH of 3.5 to 4.5, helps restore the normal acidity of the vaginal tract. At this normal pH the growth of pathogenic organisms is inhibited and the growth of the normal vaginal flora encouraged,[1] thus reducing the barriers to specific medication.

LOW pH RETENTION

Massengill Powder is buffered to retain an acid condition. In a recent clinical observation, ambulatory patients—with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for a period of 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours. Simple acid douches (vinegar or lactic acid) are quickly neutralized by an alkaline vaginal mucosa; therefore, they are somewhat unsatisfactory in maintaining the required acid pH of the vagina.[2]

LOWER SURFACE TENSION

Massengill Powder in the standard solution has a surface tension of 50 dynes/cm. as compared to that of water and simple acid solutions with 72 dynes/cm. This added property of reduced surface tension enables Massengill Powder to penetrate into and cleanse the folds of the vaginal mucosa, thus increasing the therapeutic effectiveness. Lowered surface tension makes the cell wall and cytoplasmic membrane of the infecting organism more permeable and thus more susceptible to specific therapy.[2]

SUPPLY

Massengill Powder is supplied in glass jars of the following sizes:

Small, 3 oz.
Medium, 6 oz.
Large, 16 oz.
Hospital Size, 5 lbs.

Pads of douching instructions for patient use available on request.

REFERENCES

1. Lang, W.R., Rakoff, A.E., Am. Geriatrics Soc. *1*:520 (1953).
2. Arnot, P.H., The Problem of Douching, Western Journal of Surg., Obs., and Gyn., Vol. 62, No. 2:85 (1954).

The S. E. MASSENGILL Company BRISTOL, TENNESSEE
NEW YORK SAN FRANCISCO KANSAS

Now *1* Rx

for
2-dimensional
menopausal
therapy

manages both the psychic and somatic symptoms
and *relieves* emotional stress in the menopause
treats somatic disturbances due to ovarian decline

Milprem*

*TRADE-MARK

MILTOWN® A PROVEN TRANQUILIZER + CONJUGATED ESTROGENS (EQUINE) A PROVEN ESTROGEN

SUPPLIED: Bottles of 60 tablets.

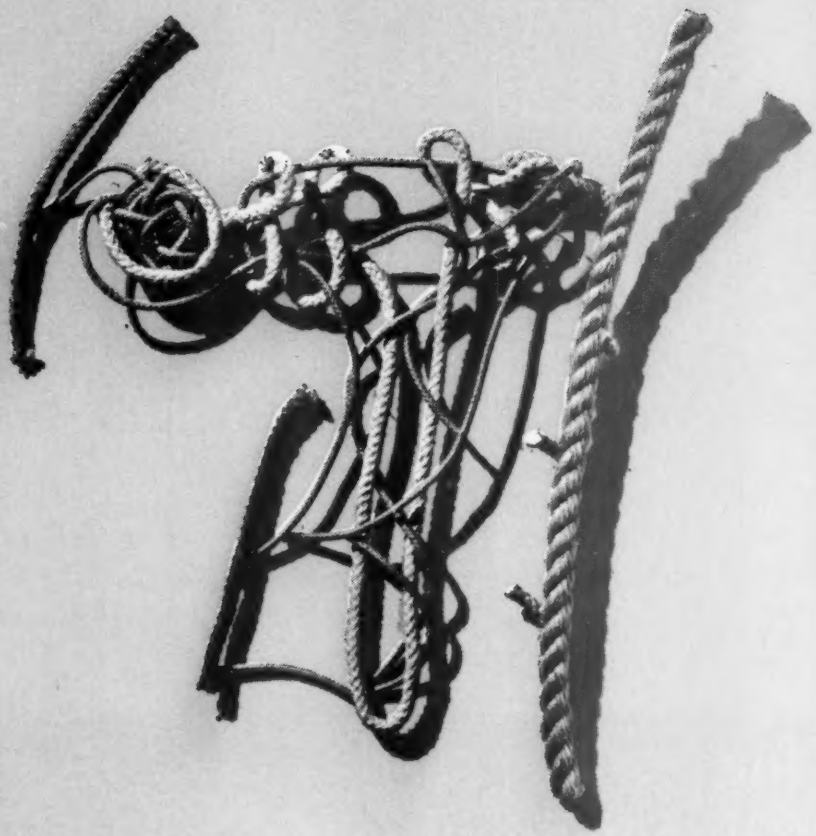
EACH TABLET CONTAINS: Miltown® (meprobamate, Wallace) .....400 mg.
2-methyl-2-**n**-propyl-1,3-propanediol dicarbamate
Conjugated Estrogens (equine) .....0.4 mg.

DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Literature and samples on request.

WALLACE LABORATORIES, *New Brunswick, N.J.*

CMP-6671-38



PYELONEPHRITIS

"A DISEASE OF THE TUBULES"[1] AS WELL AS THE GLOMERULI

In pyelonephritis, "the tubules suffer from damage to their lining cells which show cloudy swelling, granular degeneration and diminution in size. Inflammatory cells and colloid casts are found in the lumen of the tubules. Inflammatory cells are present also in the interstitial tissue. The glomeruli remain normal over a long period."

FURADANTIN®

brand of nitrofurantoin

In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

In the treatment of pyelonephritis, it is important to select an agent such as Furadantin which—in addition to its glomerular filtration—is secreted by the tubule cells. On the other hand, it has been demonstrated that sulfonamides, both free and acetylated, are excreted primarily by glomerular filtration,[2] and that "the mechanism of excretion of tetracycline is solely a glomerular filtration process without tubular involvement."[3]

In pyelonephritis . . . FURADANTIN, first

Furadantin "may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants. The importance of an agent with these characteristics that could be used for a long period in the treatment of chronic pyelonephritis has been recognized, and it is in this sphere that nitrofurantoin may have its greatest use."[4]

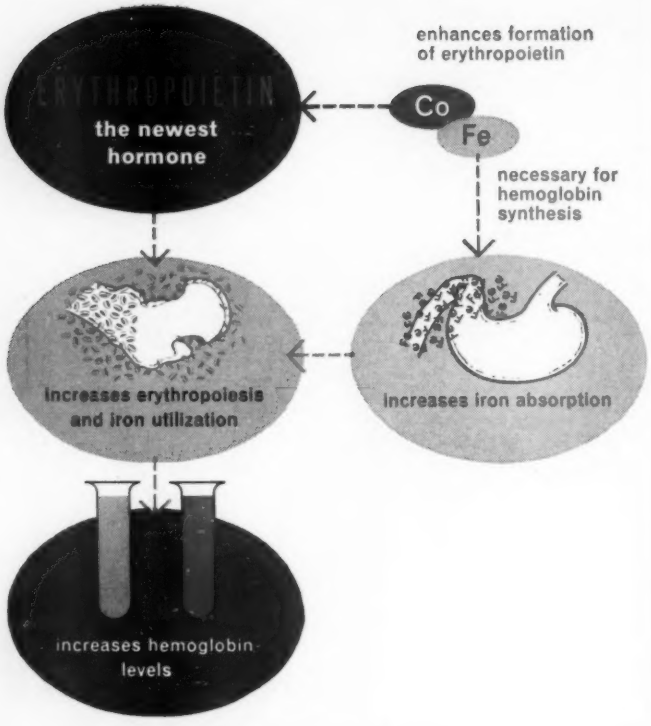
Available as Tablets, Oral Suspension and Intravenous Solution.

References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955.

C_4H_3O NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

NEW RESEARCH ON ERYTHROPOIETIN EXPLAINS CLINICAL SUPERIORITY OF



RONCOVITE®-mf

(MODIFIED FORMULA)

IN THE COMMON ANEMIAS

Elucidation of the action of erythropoietin—the erythropoietic hormone—provides a clear explanation for the observations of Holly,[1] Ausman,[2] Tevetoglu[3] and many others who have reported that in the common anemias cobalt-iron therapy results in a clinical response superior to that produced by iron alone.

Increased Iron Absorption and Utilization—Recent investigations show that cobalt enhances the formation of erythropoietin.[4,5] This hormone increases the rate of production of new red cells which, in turn, increases the rate of both iron utilization by the marrow and iron absorption from the intestine.[6]

Clinical Application—In simple *iron deficiency anemia*, 89% of patients treated with Roncovite exceeded 12 Gm. of hemoglobin per 100 cc., while only 33% of the same patients treated with iron alone for a comparable period reached this level.[2] In *anemia of pregnancy*, 98.2% of Roncovite-treated patients maintained their hematologic status; 63.8% delivered with a hemoglobin of 13 Gm. per 100 cc. or more.[1] In *anemia of infancy and childhood* an average hemoglobin level of only 8.7 Gm. per 100 cc. was attained with iron alone while the same patients subsequently reached an average hemoglobin level of 11.6 Gm. per 100 cc. with Roncovite.[3]

Roncovite-MF is the new therapeutic agent based on erythropoietin formation which translates this new research into the practical utility of full iron effectiveness with greatly decreased, better tolerated iron dosage.

Each enteric-coated, green tablet contains:

Cobalt chloride, 15 mg.
Ferrous sulfate exsiccated, 100 mg.

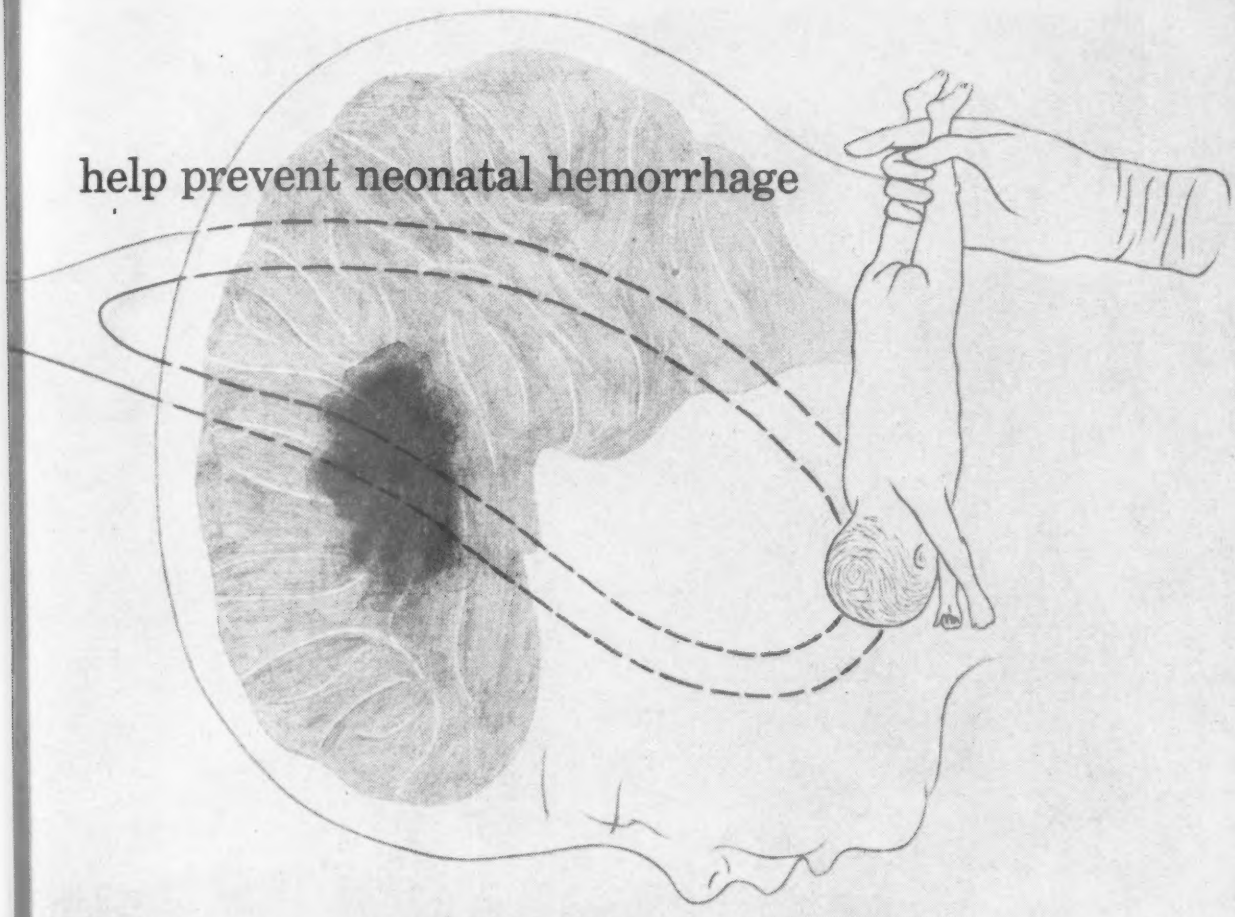
Maximum adult dosage:

one tablet after each meal and at bedtime.
Supplied: Bottles of 100 tablets.

Bibliography available on request.

LLOYD BROTHERS, INC.
CINCINNATI 3, OHIO

help prevent neonatal hemorrhage



MEPHYTON®

VITAMIN K_1

the only available preparation chemically identical with naturally-occurring vitamin K_1 . . .

*"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"**

- helps prevent "physiologic" hypoprothrombinemia, the most probable cause of hemorrhagic disease of the newborn
- helps reduce incidence of intracranial hemorrhage at birth
- if 'Mephyton' has not been given to the mother before delivery, it can be administered to the infant if birth is premature, if surgery is necessary, or if treatment of neonatal hemorrhage is required

Dosage: Hemorrhagic disease of the newborn, 0.5 to 2 mg. prophylactically to the mother is usually adequate; if actual hemorrhage occurs, up to 10 mg., repeated if necessary, may be given to the newborn.

Supplied: Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

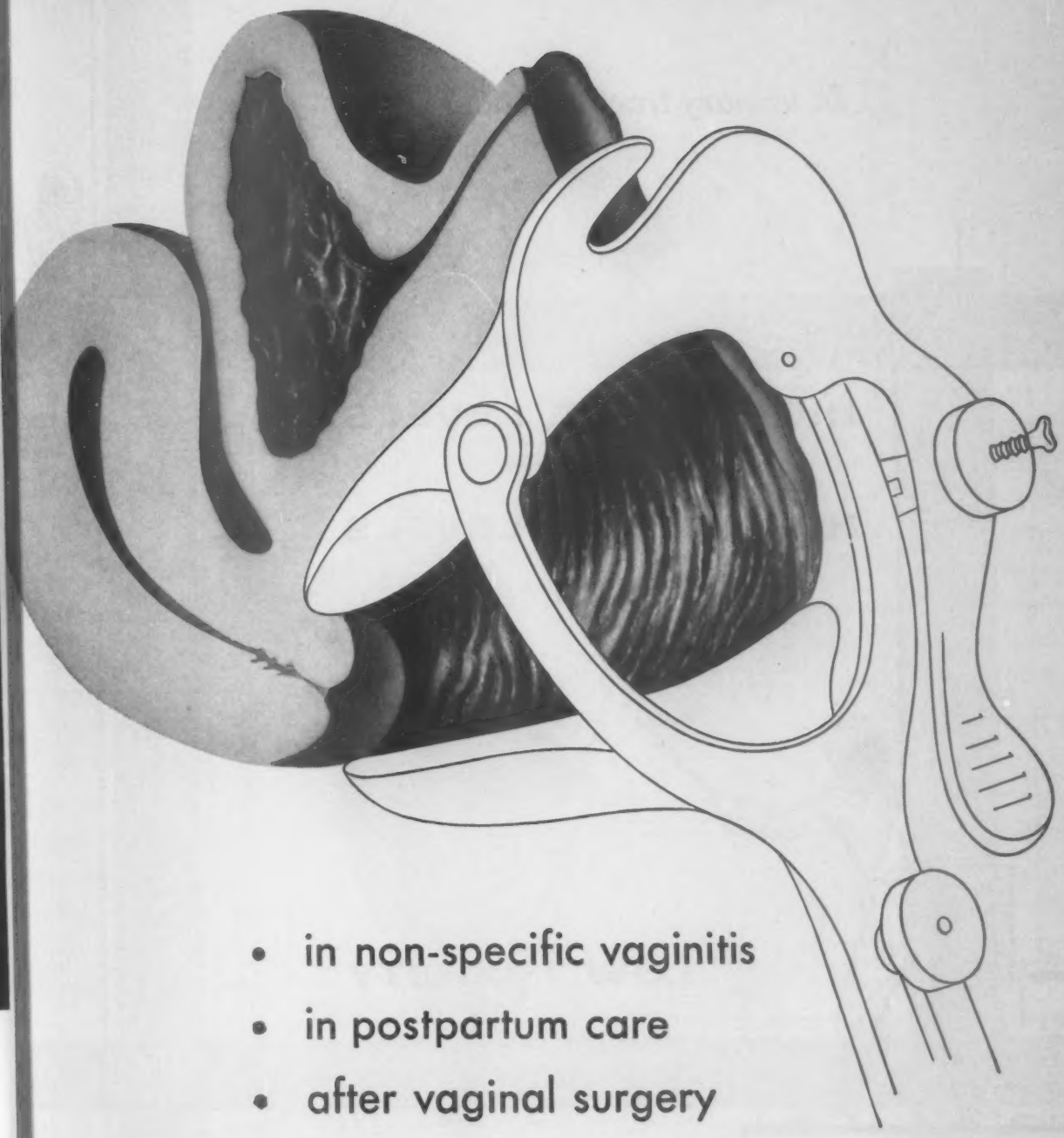
Mephyton is a trade-mark of MERCK & CO., Inc.

*Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

In
anxiety
of
pregnancy

'Miltown' relieved symptoms in 88% of pregnant women complaining of nausea, vomiting, leg cramps (refractory to calcium therapy), numbness and tingling of the extremities, headache, insomnia, anxiety, and emotional upsets.*

**Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec. 9:703, June 1957.*



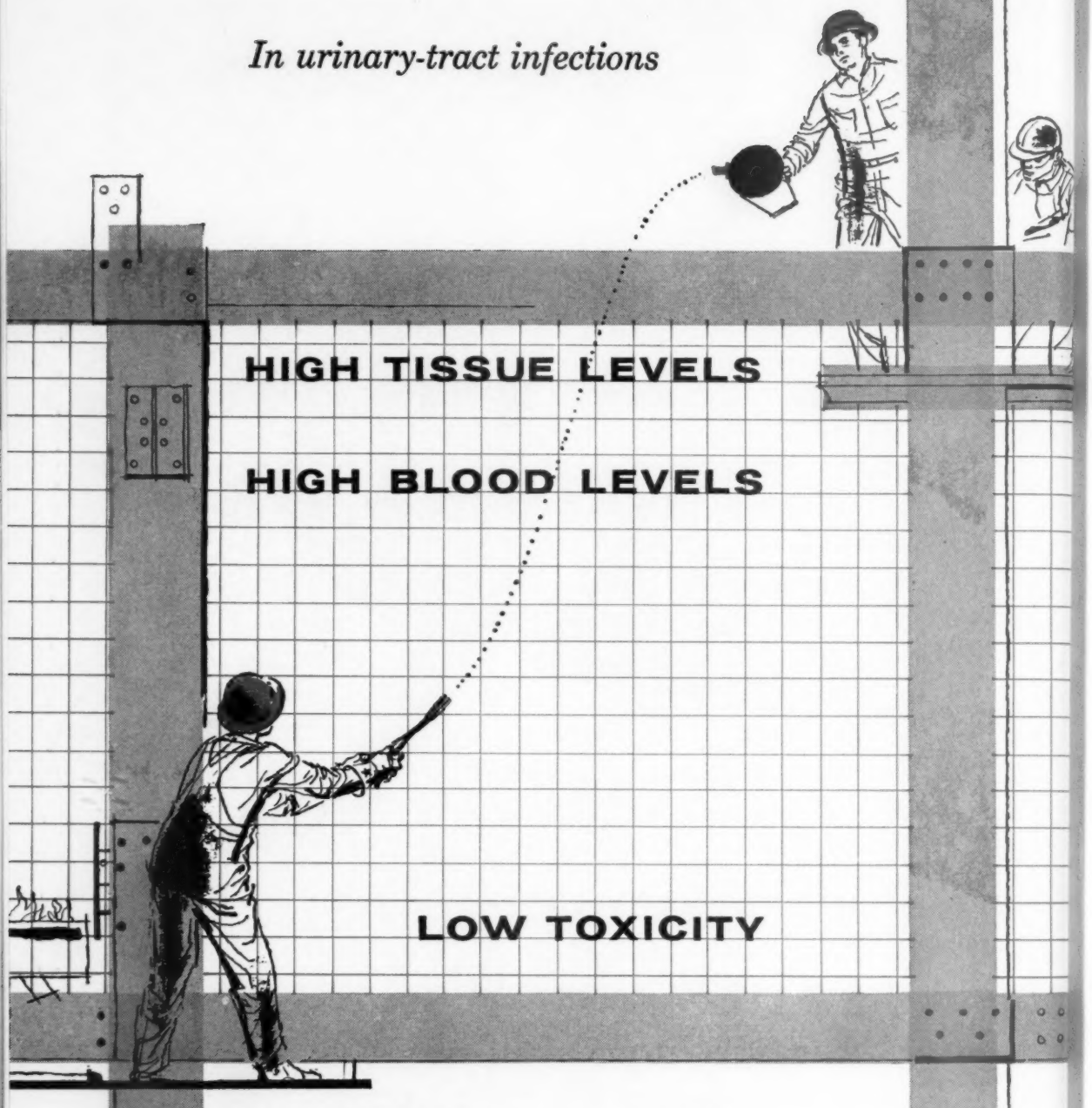
- in non-specific vaginitis
- in postpartum care
- after vaginal surgery

Triple Sulfa Cream

TRADEMARK

Ortho

In urinary-tract infections



HIGH TISSUE LEVELS

HIGH BLOOD LEVELS

LOW TOXICITY

SUSPENSION TABLETS

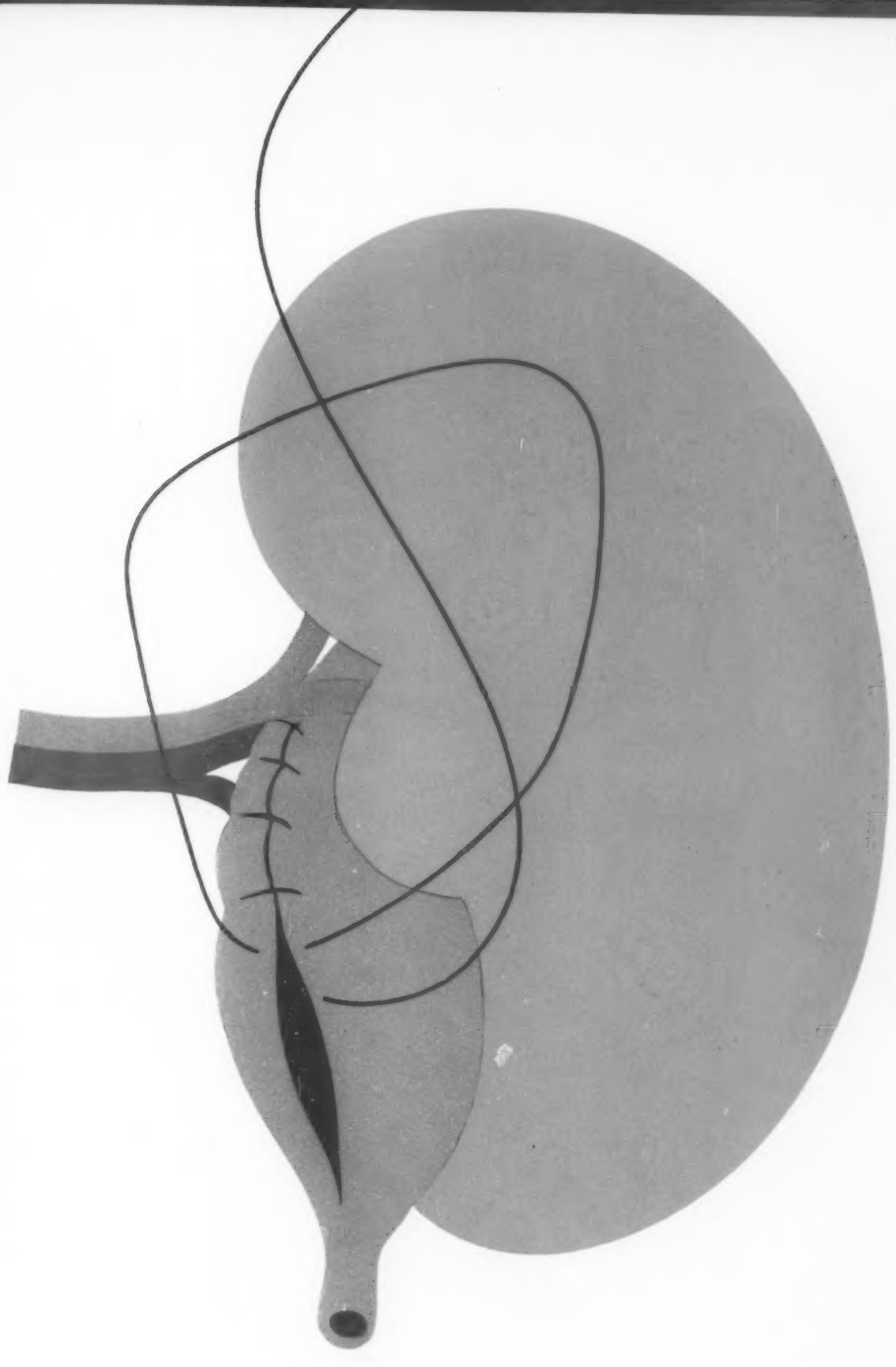
SULFOSE®

Triple Sulfonamides, Wyeth
(*Trisulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine*)

PHYSICIANS' COUNCIL · INFORMATION ON CHILD HEALTH ·

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

Wyeth®
Philadelphia 1, Pa.



setting new standards

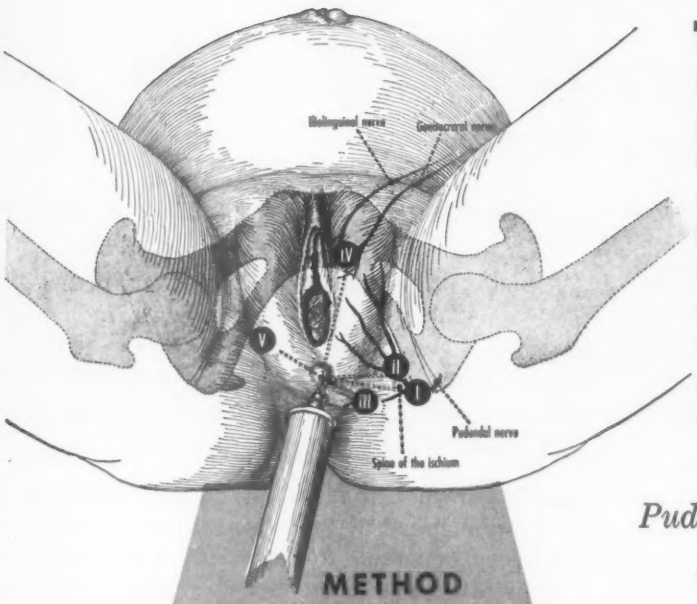
ETHICON®

sutures

NOW IN FOIL
54 INCHES
NON-BOILABLE
SURGICAL GUT
U.S.P.
STERILE
S-114
ETHICON, INC.
JUST TEAR OPEN!
Electron Sterilized
Surgical Gut and Surgical Silk
ETHICON

PONTOCAINE® *hydrochloride*

for Pudendal Block



METHOD

1. 50 cc. of 0.1 to 0.15 per cent solution of Pontocaine hydrochloride with the addition of 1 cc. of 1:1000 solution of epinephrine are used. If desired, hyaluronidase may be added.

2. The main branches of the pudendal nerve are first injected bilaterally (I, II); then points III and IV are injected, some of the solution being injected into the intermediate area.

3. Site V is for episiotomy.

The ability of Pontocaine to produce profound and exceptionally prolonged anesthesia with little likelihood of associated side reactions or local irritation makes it especially well suited for pudendal block.

Pudendal block with **PONTOCAINE** *is recommended in...*

- **normal deliveries**
- **vaginal repair**
- **perineal surgery**
- **to augment special anesthesia for perineal procedures**

SUPPLIED.

0.15 per cent solution, vials of 100 cc., and instantly soluble "Niphanoid"® form in 250 mg. ampuls.

Winthrop LABORATORIES · NEW YORK 18, N. Y.

Pontocaine (brand of tetracaine) and Niphanoid, trademarks reg. U.S. Pat. Off.

PLASMA LYTE

Now available!

THE PHYSIOLOGIC PLASMA ELECTROLYT

Provides ionic concentrations of sodium, chloride, calci and magnesium precisely as found in human plasma. the potassium concentration is twice that of norm plasma and bicarbonate is also provided in twice plasma concentration in the form of metabolizable p cursors, acetate and citrate.

INDICATIONS: Uncomplicated medical, surgical, pediatr orthopedic and urologic cases . . . to counteract dehydrati . . . to expand volume of plasma and intracellular fluid wi out distorting ionic composition . . . to prevent postoperati potassium deficiency . . . to restore normal plasma electrol values in infantile diarrhea . . . and in the management metabolic acidosis.

Because of the unique balance of its components, PLASM LYTE promotes normal fluid and electrolyte balances witho inducing potassium toxicity, tetany or metabolic acido

HOW SUPPLIED: Bottles containing 500 ml. and 1000 ml.

Where protein-sparing effect and increased caloric infusi are indicated, specify

PLASMALYTE with Travert® 10%

Bottles containing 500 ml. and 1000 ml.

BAXTER LABORATORIES, INC.

Morton Grove, Ill

DISTRIBUTED AND AVAILABLE ONLY IN THE 37 STATES EAST OF THE ROCKIES (except in the city of El Paso, Texas) THROU

AMERICAN HOSPITAL SUPPLY CORPORATIO

SCIENTIFIC PRODUCTS DIVISION GENERAL OFFICES • EVANSTON, ILLINO

iron your patients can tolerate

Rarical®

iron-calcium TABLETS

a unique new compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
- more hemoglobin in less time
- no leg cramps with this iron-calcium

Ortho

New!

IMPORTANT THERAPY

with

Specific Topical Benefits

in

Pruritus Vulvae Et Ani
Kraurosis Vulvae
Postmenopausal Vaginitis

Hist-A-Cort-E™ pH 4.7

Creme

INCORPORATED IN EXCLUSIVE ACID MANTLE® VEHICLE

ACID MANTLE® Hydrocortisone–
Estrone-Pyrilamine Maleate-Synthetic Vitamin A

providing

Epithelium Regenerative
Antiinflammatory
Antipruritic
Antikeratotic
Antiallergic
Antihistaminic
Normal-Vaginal- and Anal-Tract- pH-Restorative

action

Sig: Apply twice daily—Supply: 1 oz. tubes

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THORAZINE*

"standard" medication for patients in labor[1]

'Thorazine' was used during labor in a series of 2,093 obstetrical patients in an effort to achieve relief of pain and adequate sedation of the mother without causing respiratory depression in the infant.

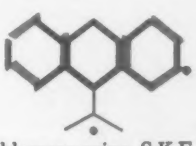
Relief of pain was good in the great majority of patients. Also, apprehension, nausea and vomiting were markedly reduced. Condition of infants at birth was good; only 2.6% required active resuscitation.

Only six patients showed significant hypotension even though 1,030 received saddle-block anesthesia.

The authors state that the good results obtained over a two-year period have made 'Thorazine' a standard drug for patients in labor.

1. Lindley, J.E.; Rogers, S.F., and Moyer, J.H.: Obst. & Gynec. *10*:582 (Nov.) 1957.

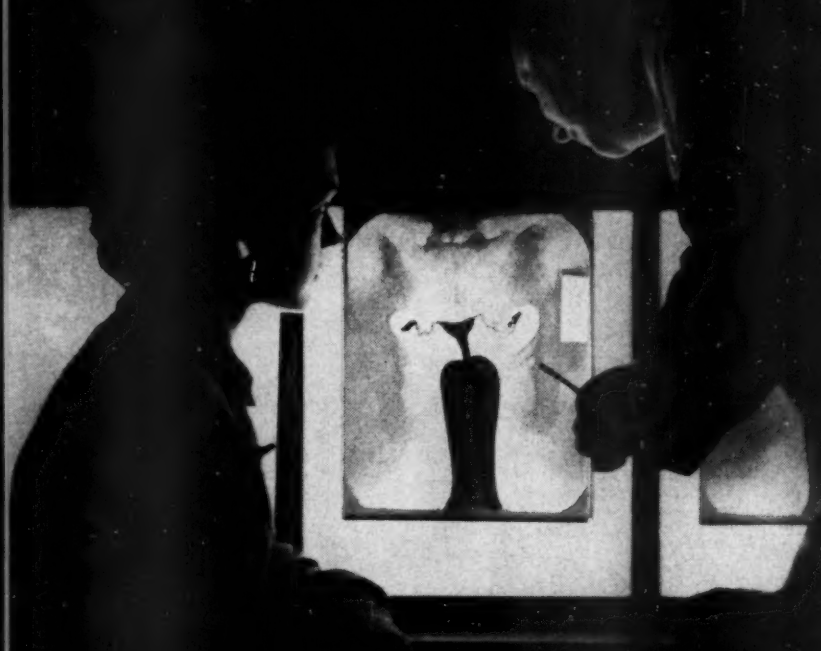
Smith Kline & French Laboratories, Philadelphia



*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

uterotubal X-rays with

far more contrast—for definitive diagnosis
far less pain—for the apprehensive patient



ETHIODOL®

(Brand of Ethiodized Oil)

advantages clinically confirmed[1,2]

- far more contrast and clarity than with aqueous media[1,2]
- free-flowing viscosity—fluidity similar to distilled water[1]
- absence of notable pain[1,2]
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- optimal absorption characteristics[1]
- more information than Rubin test for sterility diagnosis[1,2]

ETHIODOL,® brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10-cc. ampules, boxes of two. A development of Guerbet Laboratories.

sources: 1. Steinberg, W.: Am. J. Obst. & Gynec. 75:144, 1958.
2. Becker, S.: J. Am. M. Women's A. 12:332, 1957.

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TYPICAL IMFERON RESPONSES

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INTRAMUSCULAR IRON-DEXTRAN COMPLEX

CHRONIC BLOOD LOSS:

"...this patient did not receive any transfusion of blood or any hematinic other than the intramuscular dose of iron. His initial concentration of hemoglobin measured 5.8 gm. per 100 cc. of blood and in spite of operation (hemorrhoidectomy) and further loss of blood the concentration increased to 12.2 gm. within less than 3 weeks. Concomitantly with the hematologic improvement there was clinical improvement and subsidence of the initial primary symptoms [unusual fatigability, dyspnea, palpitation on exertion]."[1]

INTOLERANCE TO ORAL IRON:

"...she had an excellent response with a reticulocyte peak of 5.3 per cent on the seventh day, and a complete disappearance of the anemia and conversion from hypochromic to normochromic cells by the end of two months. She experienced remarkable improvement in pep and sense of well-being coincident with the alleviation of her anemia."[2]

(1) Hagedorn, A. B.: Proc. Staff Meet. Mayo Clin. 32:705 (Dec. 11) 1957.
(2) Best, W. R.; Louis, J., and Limarzi, L. R.: M. Clin. North America (Jan.) 1958, p. 3.

Supplied: 2-cc. and 5-cc. ampuls, boxes of 4. Physician's directions in every box. There are 50 mg. of elemental iron per cc. Request brochure NDA 17, Imferon.

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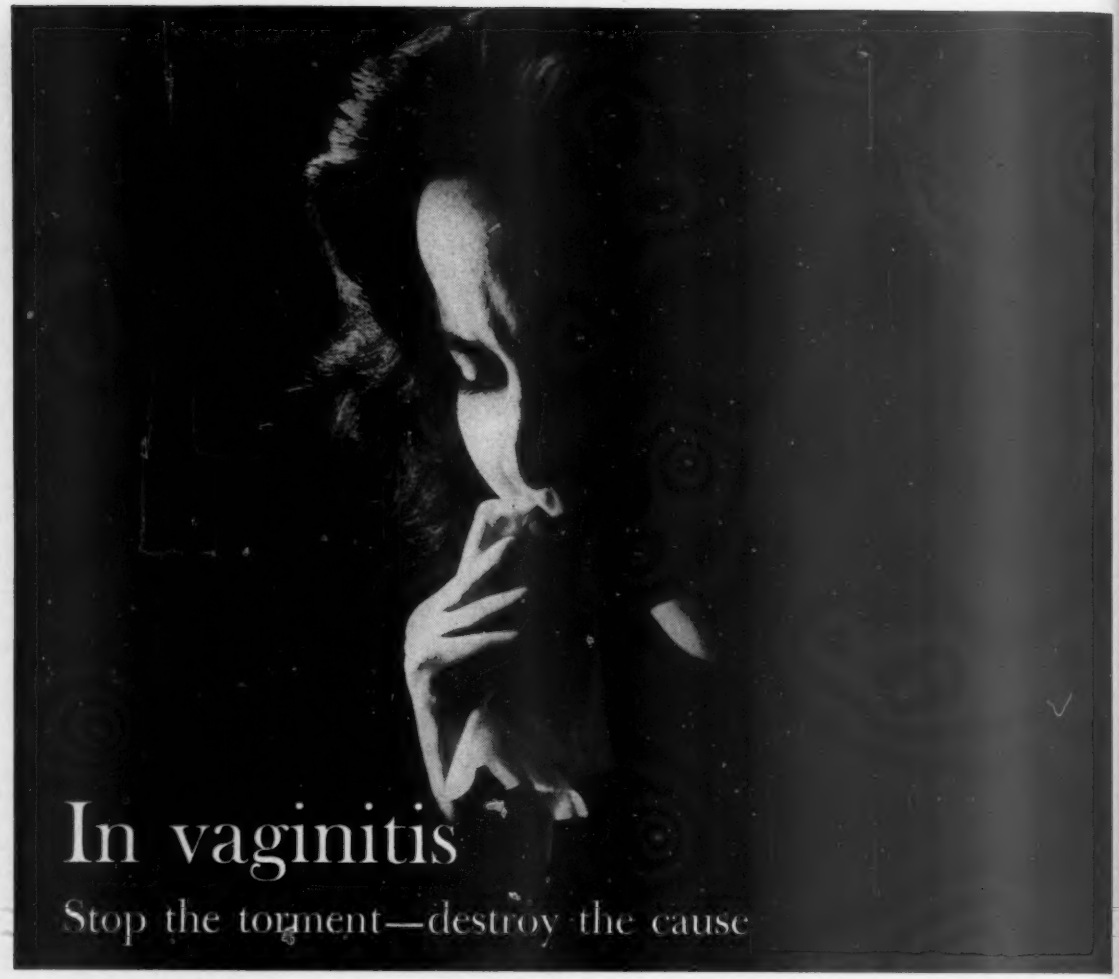

AVC

Improved

in trichomonal vaginitis –
"... the most effective treatment available."[1]

in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]

in mixed infection –
"... the most effective treatment of endocervicitis. ..."[3]

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.[1] Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

Indications: Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

Products of Original Research

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

BIBLIOGRAPHY

(1) Noojin, R. O.: South. M. J. *49*:149, *162*:1379, 1956. (3) Goldman, L.; Flatt, *25*:75, 1955. (4) Frank, L., and Stritzler, (5) Robinson, R. C. V., and Robinson, (6) Canizares, O.; Shatin, H., and Rosen 1955.

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NAME **METI-DERM® CREAM 0.5%**

DESCRIPTION 5 mg. prednisolone, free alcohol, in each gram—nonstaining, water-washable base—exerts a therapeutic effect in presence of an exudate without being occlusive.

supplied: 10 Gm. tube.

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prednisolone, free alcohol, in a water-washable base

PACKAGING: METI-DERM Cream 0.5%, 10 Gm. tube.

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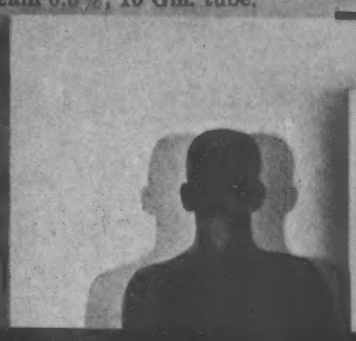
WHEN SCRATCHING

Meti-Derm

PICAL CREAM METI-DERM Cream

ic action in the affected area. No system

and weight gain, have been reported wi



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TI-DERM

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STRONGEST

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IN SKIN RASHES

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METI-STEROID E

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'DIURIL'

(CHLOROTHIAZIDE)

FORD, R. V., Rochelle, J.B.III, Handley, C. A., Moyer, J. H. and Spurr, C. L.: J.A.M.A. **166**:129, Jan. 11, 1958.

". . . in premenstrual edema, convenience of therapy points to the selection of chlorothiazide, since it is both potent and free from adverse electrolyte actions." In the vast majority of patients, 'DIURIL' relieves or prevents the fluid "build-up" of the premenstrual syndrome. The onset of relief often occurs within two hours following convenient, oral, once-a-day dosage. 'DIURIL' is well tolerated, does not interfere with hormonal balance and is continuously effective—even on continued daily administration.

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SUPPLIED: 250 mg. and 500 mg. scored tablets 'DIURIL' (chlorothiazide); bottles of 100 and 1,000.

DIURIL is a trade-mark of Merck & Co., Inc.

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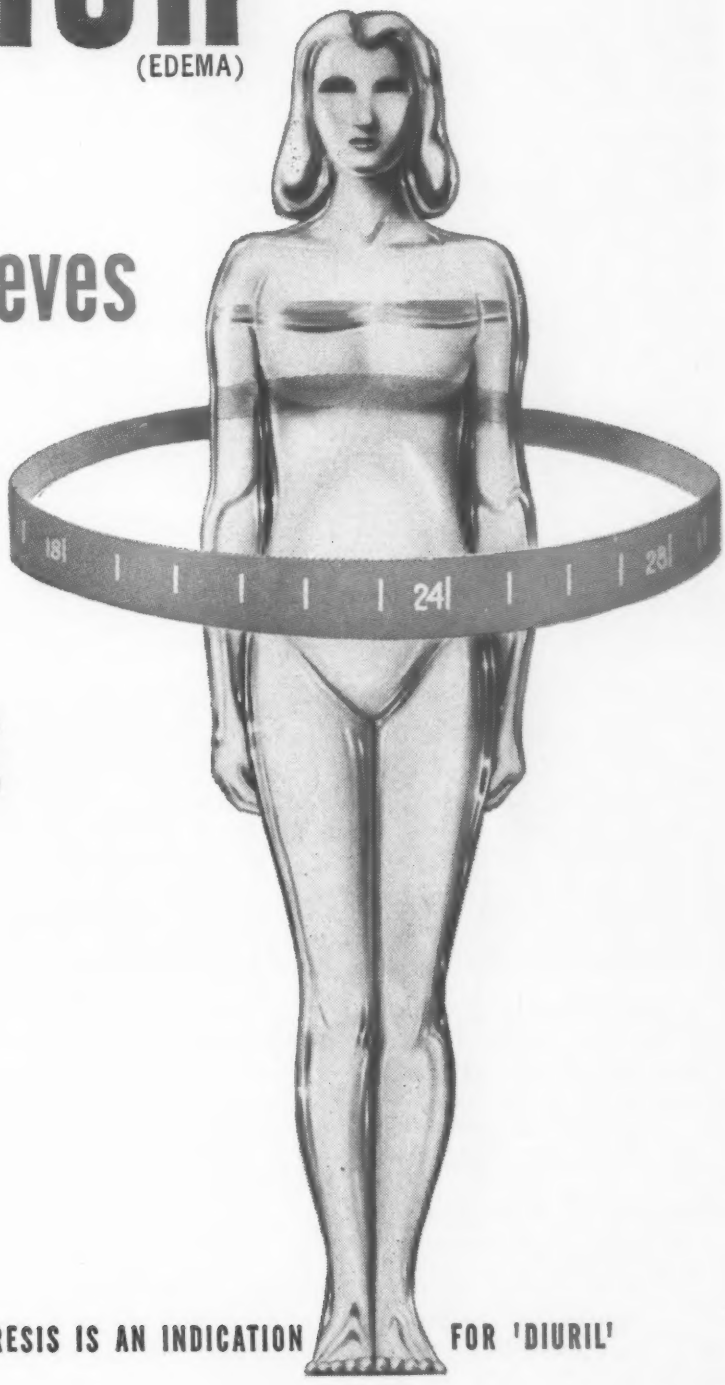
Discomfort



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Many such hypertensives have been on *Rauwiloid* for 3 years and more*

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just two tablets at bedtime
After full effect one tablet suffices

Enhances safety when more potent drugs are needed.

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Both combinations in convenient single-tablet form.

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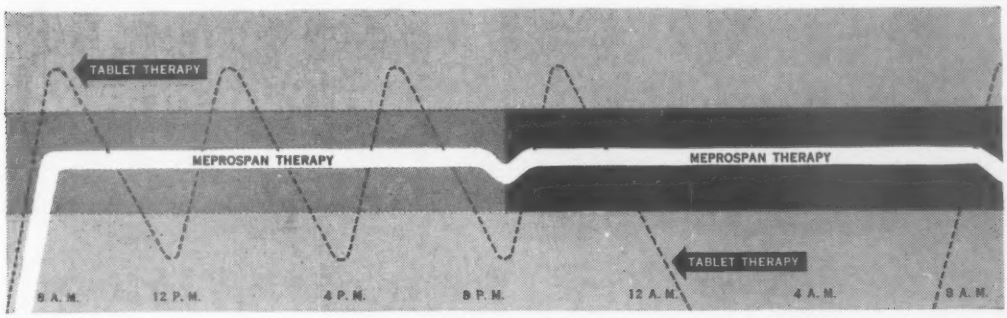
New... meprobamate prolonged release capsules

Evenly sustain relaxation of mind and muscle 'round the clock



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RELIEVE ANXIETY, TENSION AND SKELETAL MUSCLE SPASM THROUGHOUT THE DAY.

TWO MEPROSPAN CAPSULES AT BEDTIME
PROVIDE UNINTERRUPTED SLEEP THROUGHOUT THE NIGHT.

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MEPROBAMATE IN **PROLONGED RELEASE** CAPSULES

- maintains constant level of relaxation
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Dosage: Two Meprospan capsules q. 12 h.
Supplied: Bottles of 30 capsules.
Each capsule contains:
Meprobamate (Wallace) ..... 200 mg.
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WEIGHT REDUCTION: Obese patients may resist dieting because they fear losing the emotional security often involved in overeating. **AMBAR** helps them hold the diet line by giving them a more alert, brighter outlook. **WITHOUT JITTERS:** Methamphetamine, a potent **CNS** augmenter, produces less cardiovascular effect than amphetamine. In **AMBAR** it is combined with just enough phenobarbital to prevent overstimulation. **AMBAR EXTENTABS** provide 10-12 hours of appetite suppression in one controlled-release, extended-action tablet: methamphetamine hydrochloride, 10.0 mg.; phenobarbital (1½ gr.) 64.8 mg. **AMBAR TABLETS** for conventional dosage or intermittent therapy contain methamphetamine hydrochloride, 3.33 mg.; phenobarbital (⅓ gr.) 21.6 mg. **A. H. ROBINS COMPANY, INC.**, Richmond, Virginia, Ethical Pharmaceuticals of Merit Since 1878

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methamphetamine and phenobarbital
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FILIBON helps

her meet the nutritional demands of pregnancy in today's active life by supplying full vitamin-mineral supplementation, plus . . .

- A phosphorus-free formula
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to keep her on the regimen you prescribe

- the attractive FILIBON Jar
- the FILIBON capsule, small and easy to swallow
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Each soft-shell FILIBON capsule contains:

Vitamin A	4,000 U.S.P. Units	Iron (as Fumarate)	30 mg.
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Thiamine Mononitrate (B_1)	3 mg.	Fluorine (CaF_2)	0.015 mg.
Pyridoxine (B_6)	1 mg.	Copper (CuO)	0.15 mg.
Niacinamide	10 mg.	Iodine (KI)	0.01 mg.
Riboflavin (B_2)	2 mg.	Potassium (K_2SO_4)	0.835 mg.
Vitamin B_{12}	2 mcgm.	Manganese (MnO_2)	0.05 mg.
Ascorbic Acid (C)	50 mg.	Magnesium (MgO)	0.15 mg.
Vitamin K (Menadione)	0.5 mg.	Molybdenum ($Na_2MoO_4.2H_2O$)	0.025 mg.
Folic Acid	1 mg.	Zinc (ZnO)	0.085 mg.
Ferrous Fumarate	90 mg.	Calcium Carbonate	575 mg.

in the picture . . . during pregnancy

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PHOSPHORUS-FREE PRENATAL VITAMIN-MINERAL SUPPLEMENT LEDERLE

DOSAGE/ one or more capsules daily

SUPPLIED/ attractive re-usable bottles of 100 capsules

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*Reg. U. S. Pat. Off.

Most effective when used preoperatively

Adrenosem®*

SALICYLATE

(Brand of carbazochrome salicylate)

to control oozing and bleeding

As one clinician states: "Blood loss may be hidden temporarily after closure of the thoracic or abdominal cavities, even though drains are in place. Obstruction to outflow through these drains can occur, and bleeding is not apparent.

"There are certain clinical situations in which prolonged and profound oozing of blood may occur."[1]

Published reports[2-6] over the last five years emphasize the value of Adrenosem preoperatively—to control oozing and bleeding and provide a clearer operative field.

Adrenosem does not affect blood pressure, cardiac rate or output, blood clotting mechanism, massive hemorrhage, or arterial bleeding.[7]

Supplied in ampuls, tablets and as a syrup.

*U.S. Pat. 2581850, 250629

THE S. E. MASSENGILL COMPANY

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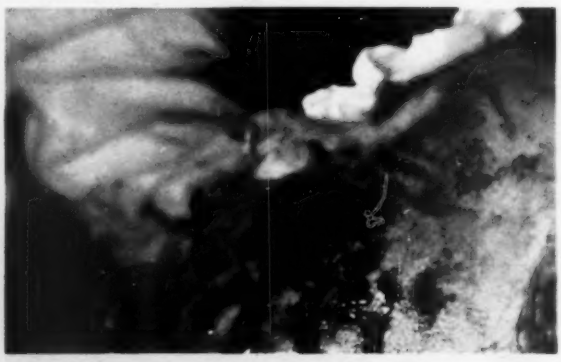
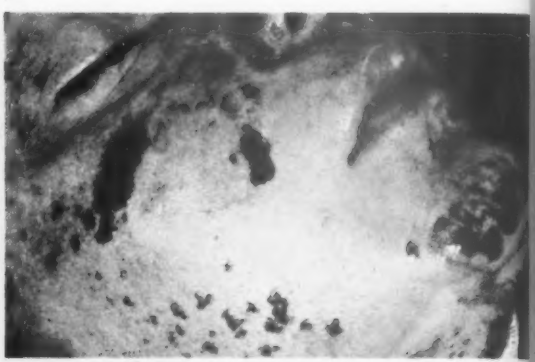
One of the many procedures where Adrenosem® SALICYLATE has been especially effective when used preoperatively

The photographs below are of two typical cases in 200 dermabrasion procedures[4] over a period of two years.



Case #1 Left cheek untreated



Case #1 Right cheek, after treatment with Adrenosem

Case #2 Left cheek untreated

Case #2 Right cheek, after treatment with Adrenosem

Write for literature describing the action and uses of Adrenosem Salicylate

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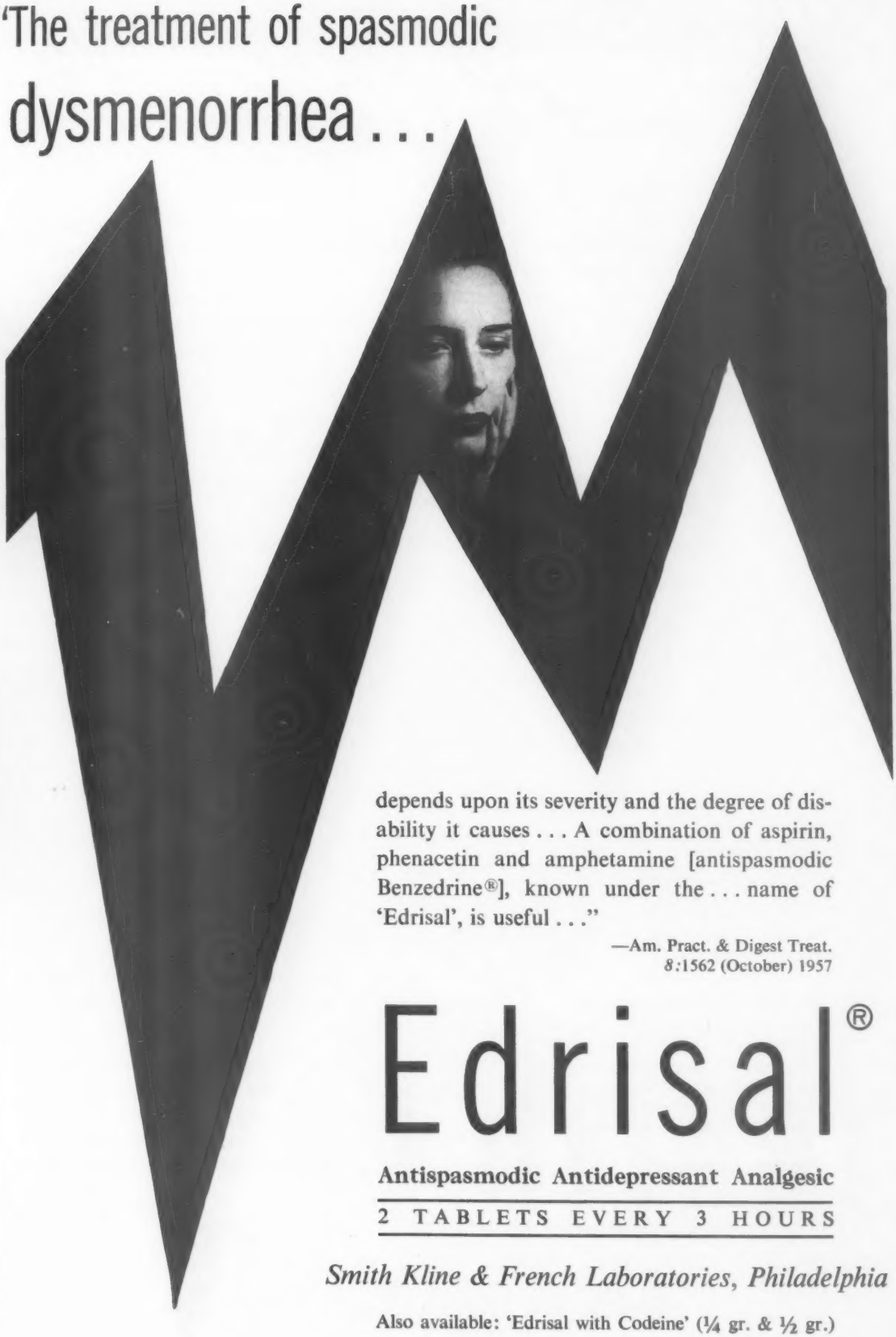
1. *Dripps, R.D.: Hazards of the Immediate Postoperative Period, J.A.M.A. 7:795 (Oct. 19, 1957) [This reference reviews postoperative hazards, and does not refer to Adrenosem Salicylate]*
2. *Ersner, M.S., and Lerner, S.S.: M. Clin. North America 40:1749 (Nov., 1956)*
3. *Peele, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat, N. Carolina M.J. 17:98 (March, 1956)*
4. *Brown, W.S.: The Use of Adrenosem Salicylate Control Postoperative Bleeding in Plastic Surgery Dermabrasion, Northwest Medicine. In Press.*
5. *Wilkins, B.D.: Gastrointestinal Bleeding as Seen the Proctologist, J.A.M.A. 163:1214 (April 6, 19*
6. *Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N. State J. Med. 55:886 (Mar., 1956)*
7. *N.N.R., 1957, p. 265*

"The treatment of spasmodic dysmenorrhea . . .



depends upon its severity and the degree of disability it causes . . . A combination of aspirin, phenacetin and amphetamine [antispasmodic Benzedrine®], known under the . . . name of 'Edrisal', is useful . . ."

—Am. Pract. & Digest Treat. *8*:1562 (October) 1957

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Antispasmodic Antidepressant Analgesic

2 TABLETS EVERY 3 HOURS

Smith Kline & French Laboratories, Philadelphia

Also available: 'Edrisal with Codeine' (¼ gr. & ½ gr.)

When "Breakfast Anorexia" must be Overcome

Anorexia upon arising must often be dealt with as part of a therapeutic regimen. In addition to the well-known syndrome of early pregnancy, several other causes of "breakfast anorexia" are recognized. Generally psychological in character, they include fear or lack of enthusiasm in facing the day, distaste or intolerance for the fried and fatty foods commonly served at breakfast, and habit patterns such as late rising with the inevitable morning rush. Obese patients who "cannot" eat breakfast tend to overeat during the day in order to overcome the deficit.

When "breakfast anorexia" must be overcome, physicians find that a dish of steaming oatmeal as the main food at breakfast is a great help in the solution of this problem. Its inviting warmth and delicious taste make the oatmeal dish appealing even when appetite is poorest. It also provides readily available energy for a morning of productive work; it helps to allay hunger throughout the morning; it makes a notable contribution to the day's nutritional needs; it is low in fat, and is easily digested.

Oatmeal is richer in protein than all other whole-grain breakfast cereals. It ranks among the highest in thiamine, and contributes other B vitamins as well. It is outstanding for its iron content.

The correction of "breakfast anorexia" can be made easier in many ways by a morning dish of oatmeal and milk, so quickly and easily prepared, and so gratifying.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

IN PRENATAL NUTRITION
In the aim for optimal nutrition without undue weight gain during the entire prenatal period, oatmeal serves well as a universally accepted food high in nutrient value without "empty" calories.

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AFTER THE BLESSED EVENT

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AEROSOL SPRAY

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced*

Formula: benzocaine 4.7% benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (DOHO PROCESS)

Available in 3 sizes:

PRESCRIPTION: new 3 oz. (for individual therapy in hospital & home)

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Other indications responding to DERMOPLAST's quick, therapeutic pain relief:

perineal suturing
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pruritus vulvae
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Supporting clinical data on request

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CONCLUSIONS:

after 2 years of extensive clinical use of...

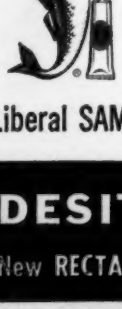
RECTAL DESITIN® OINTMENT

"it has fulfilled better than any previously tried medicaments all the qualifications" expected of a proctologic ointment[1]

"promotes smooth epithelization and healthy granulation tissue and accelerates healing."[1]

- Specially formulated for prolonged, unusual efficacy in relieving pain, itching, irritation and inflammation in non-surgical HEMORRHOIDS, PRURITUS ANI, FISSURES, PERIANAL DERMATITIS, PAPILLITIS, etc. Non-sensitizing.

Formula: **RECTAL** DESITIN OINTMENT contains high grade Norwegian cod liver oil, zinc oxide, lanolin, talcum, sodium lauryl sulfate, petrolatum q.s. Does **not** contain local anesthetics, narcotics, or "caine" drugs which might mask serious anorectal disorders.



Available on your prescription in tubes of 1½ oz., with a safe, flexible applicator

Liberal SAMPLE supply on request

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New RECTAL DESITIN OINTMENT is not to be confused with regular DESITIN OINTMENT

1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.

extra protection for every conception

Decidual bleeding due to capillary fragility leads to abortion

Hesper-C Prenatal

with capillary-protective factors plus vitamins-minerals

a precaution in every pregnancy
a necessity in habitual abortion[1,2]

Routine care during pregnancy should include protection against decidual bleeding. To guard against spontaneous and habitual abortion, Hesper-C Prenatal provides the essential capillary-protective factors (hesperidin complex and ascorbic acid) *plus* the supplemental vitamins and minerals required during gestation.

The usual daily dosage (2 capsules t.i.d.) provides:			
HESPERIDIN COMPLEX	600 mg.	Thiamine Mononitrate	7.5 mg.
ASCORBIC ACID	600 mg.	Riboflavin	4.5 mg.
Ferrous Gluconate (15 mg. iron)	130 mg.	Nicotinamide	30.0 mg.
Calcium Pantothenate	6 mg.	Vitamin B_{12}	4.5 mcg.
Calcium Carbonate (500 mg. calcium)	1.25 Gm.	Folic Acid	0.3 mg.
Vitamin A Acetate	6,000 U.S.P. Units	Pyridoxine Hydrochloride	10.0 mg.
Vitamin D_2	1,200 U.S.P. Units	Copper Sulfate (3.0 mg. copper)	12.0 mg.
		Potassium Iodide (0.3 mg. iodine)	0.4 mg.

Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

1. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.
2. Dill, L. V.: M. Ann. District of Columbia 23:667, 1954.

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

Products of Original Research

HCP 1800/57

not only for protection

as the vaginal menstrual guard of choice...

but also for professional use

to retain vaginal and cervical medications after treatment and between office visits.

to protect against seepage after cervical biopsy or cauterization.

to absorb discharges or abnormal secretions.

Three Absorbencies—REGULAR, SUPER, JUNIOR—for varying requirements.

Made of pure surgical absorbent cotton—readily available and economical.

COMFORTABLE • CONVENIENT • SAFE

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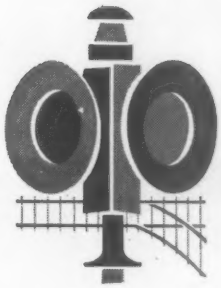
announcing...oral iron under
chelate control for a
SURER HEMATINIC EFFECT



confirmed in J.A.M.A.*

"administration of iron with food...reduce[s] the amount of iron available for hemopoiesis and limit[s] the effectiveness of treatment..."*

"the presentation of iron to the system as a chelate complex [iron choline citrate] permits its administration between meals..."*

CHĒL-IRON

BRAND OF IRON CHOLINE CITRATE† TRADEMARK

CHELATED IRON permits optimal uptake as physiologically required...no iron lost through precipitation...therapy uninterrupted by intolerance

notably effective...exceptionally well tolerated...safest iron to have in the home

■ CHĒL-IRON TABLETS/where iron alone is indicated ■ CHĒL-IRON PEDIATRIC DROPS/can be mixed with milk or formula, will not stain teeth ■ CHĒL-IRON PLUS TABLETS/chelated iron plus B_{12} with intrinsic factor, folic acid, pyridoxine, other essential B vitamins, and C.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685 Apr. 5, 1958.
†U.S. Pat. 2,575,611

Kinney® KINNEY & COMPANY, INC. COLUMBUS, INDIANA

an entirely new concept in broad-spectrum therapy

COSA

Pfizer | Pfizer

what is COSA

Cosa is an abbreviation for glucosamine, a basic substance older than man himself, found throughout the human body and in the whole spectrum of nature—lobster shells . . . mother's milk . . . eggs . . . gastric mucin. . . . It achieved new importance when Pfizer scientists discovered that this interesting compound provided the following significant advantages when added to antibiotics such as tetracycline and oxytetracycline:

1. Higher, faster antibiotic blood levels[1]
2. More consistent high antibiotic blood levels[2]
3. Effective, well-tolerated broad-spectrum therapy[3,4,5]
4. Safe, physiological potentiation with glucosamine, a nontoxic human metabolite[6,7,8]

References: **1.** Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 5:52 (Jan.) 1958. **2.** Carlozzi, M.: Ibid. 5:146 (Feb.) 1958. **3.** Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. **4.** Stone, M. L.; Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy 5:322 (May) 1958. **5.** Combleet, T.; Chesrow, E., and Barsky, S.: Ibid. 5:328 (May) 1958. **6.** West, R., and Clarke, D. H.: J. Clin. Invest. 17:173 (March) 1938. **7.** Jimenez-Diaz, C.; Aguirre, M., and Arjona, E.: Bull. Inst. M. Res. Madrid 6:137 (Oct.-Dec.) 1953. **8.** Lerman, S.; Pogell, B. M., and Lieb, W.: A.M.A. Arch. Ophth. 57:354 (March) 1957.

Your patients will do better when you choose COSA antibiotics

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

This excellently tolerated formulation provides highest, fastest blood levels of tetracycline, the most widely used broad-spectrum antibiotic. Capsules (black and white) 250 mg. and 125 mg.; orange-flavored Oral Suspension, 125 mg. per 5 cc.

COSA-SIGNEMYCIN*

TRIACETYLOLEANDOMYCIN GLUCOSAMINE-POTENTIATED TETRACYCLINE

Provides broad-spectrum antibiotic activity (Cosa-Tetracyn) *plus* triacetyloleandomycin effectiveness against many organisms resistant to currently used antibiotics. Recommended for home or office where sensitivity testing is difficult or impractical. Capsules (green and white) 250 mg. and 125 mg.

COSA-TERRAMYCIN

OXYTETRACYCLINE WITH GLUCOSAMINE

A proven standard in antibiotic therapy for over 8 years now significantly improved through (1) glucosamine potentiation, (2) additional recrystallizations for maximum purity. Capsules (yellow) 250 mg. and 125 mg.; peach-flavored Oral Suspension, 125 mg per 5 cc.

Researching the future—today

Pfizer PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

*Trademark

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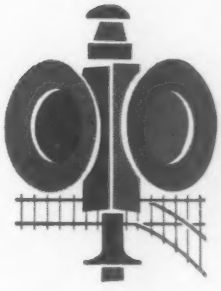
announcing...oral iron under chelate control for VIRTUAL FREEDOM FROM G.I. INTOLERANCE



confirmed in J.A.M.A.*

"One of the major difficulties associated with iron therapy is that of the occurrence of gastrointestinal disturbances..."*

"iron choline citrate, a chelated form of iron, possesses outstanding qualities in terms of freedom from undesirable gastrointestinal effects."*

CHĒL-IRON

BRAND OF IRON CHOLINE CITRATE† TRADEMARK

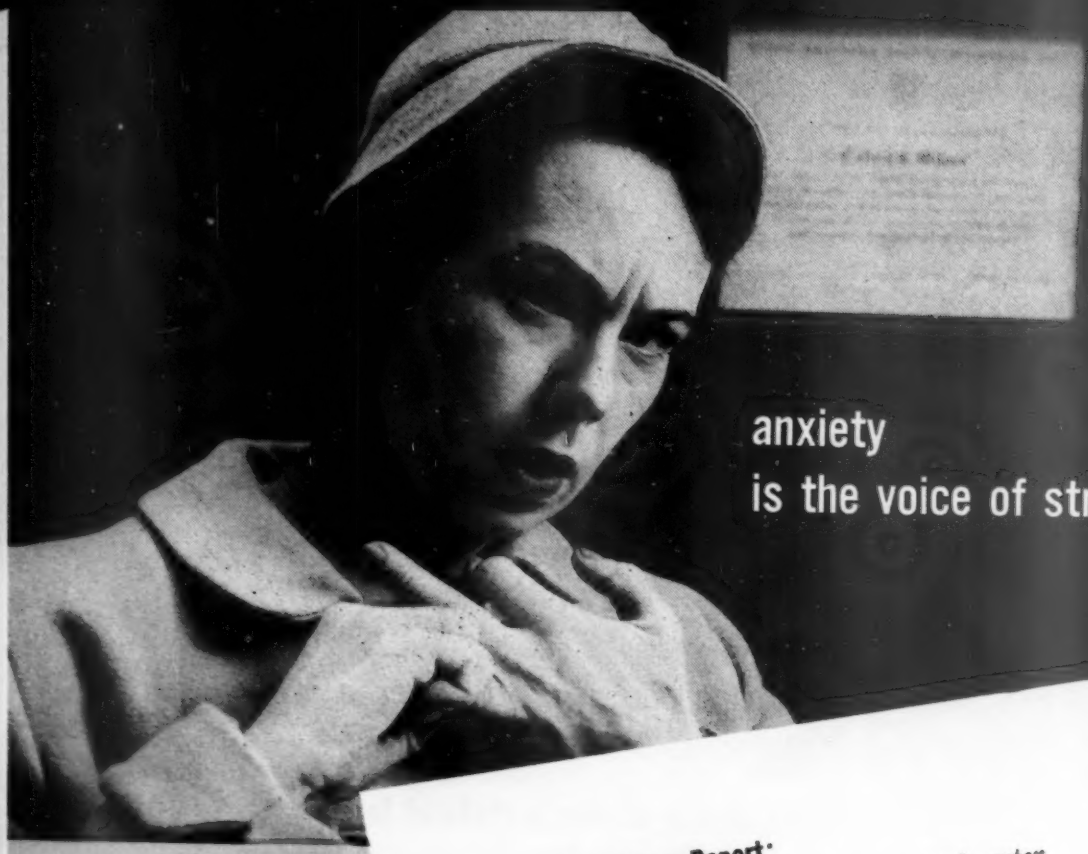
CHELATED IRON...remains in solution...no irritating ionization or precipitation...acceptable even to peptic ulcer patients...can be taken on an empty stomach

exceptionally well tolerated...notably effective...safest iron to have in the home

■ CHĒL-IRON TABLETS/three tablets supply 120 mg. elemental iron ■ CHĒL-IRON PEDIATRIC DROPS/each cc. supplies 16 mg. elemental iron in a flavored, nonalcoholic vehicle ■ CHĒL-IRON PLUS TABLETS/three tablets supply 72 mg. elemental iron plus B_{12} with intrinsic factor, folic acid, pyridoxine, other essential B vitamins, and C.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.
†U. S. Pat. 2,575,611

Kinney® KINNEY & COMPANY, INC. COLUMBUS, INDIANA



anxiety
is the voice of stress

Representative Case Report:
Patient in first trimester

Primipara with emotional instability and behavioral changes dating from early weeks of pregnancy. Patient was anxious and fretful, and complained of restlessness, insomnia, frequent crying, and tension headache. EQUANIL allayed these symptoms of anxiety and tension, and the patient's outlook became cheerful.

pregnancy is a state of stress

EP
S

EQUANIL
Meprobamate
PHENERGAN® HCl
Promethazine HCl
SPARINE® HCl
Promazine HCl

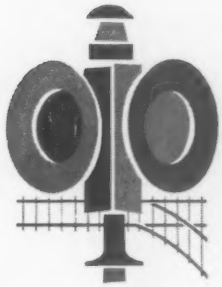
A Wyeth normotropic drug for nearly every patient under stress

Wyeth
Philadelphia 1, Pa.

Equanil®
Meprobamate

Relieves tension—mental and muscular

announcing...oral iron under chelate control for PROTECTION AGAINST IRON POISONING



confirmed in J.A.M.A.*

"acute toxicity of iron must now be seriously considered... an increasing number of near-fatal and fatal poisonings have been reported after the accidental ingestion of iron by children."*

"The chelation of iron minimized its toxicity and provided a high factor of safety against fatal poisoning."*

CHĒL-IRON

BRAND OF IRON CHOLINE CITRATE† TRADEMARK

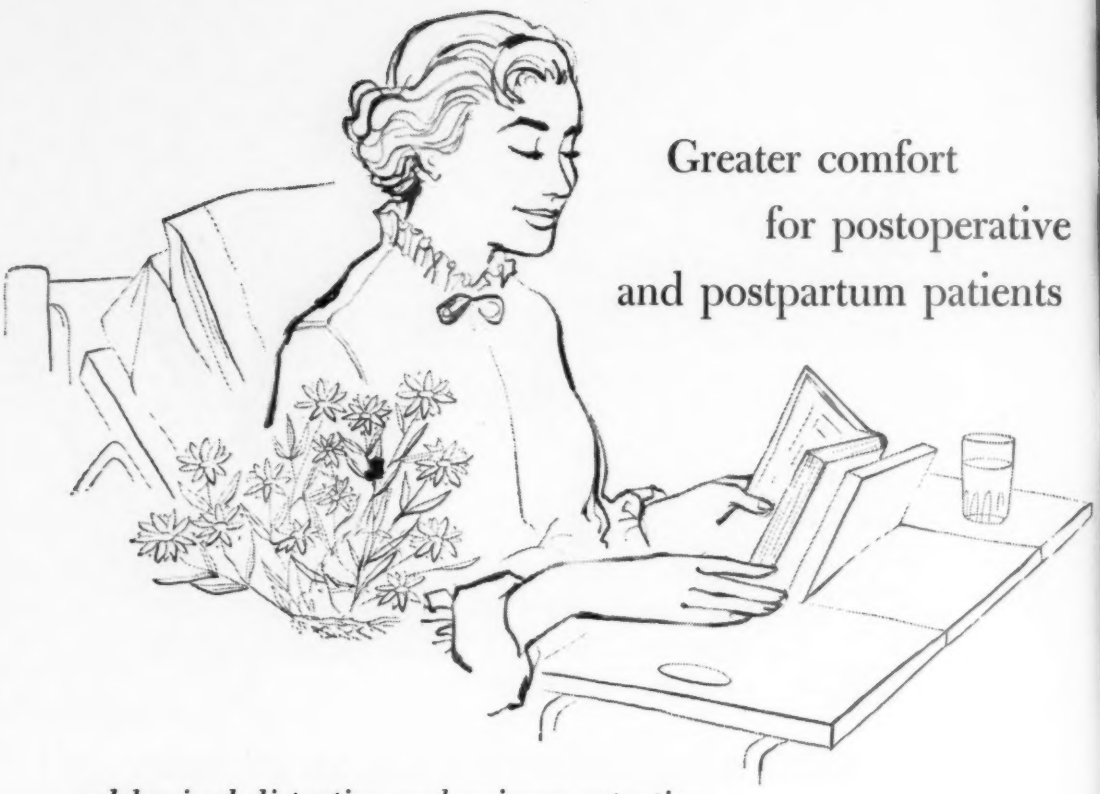
CHELATED IRON... minimizes excessive systemic iron uptake—even on accidental overdosage—without impairing hematinic response

safest iron to have in the home... exceptionally well tolerated... notably effective

DOSAGE FORMS	DOSAGE
CHĒL-IRON TABLETS Bottles of 100	Adults, 1 or 2 tablets t.i.d. Children, 1 tablet t.i.d.
CHĒL-IRON PEDIATRIC DROPS 30-cc. bottles with graduated dropper	For prophylaxis in infants and children up to 6 years, 0.5 cc. daily (full M.D.R.). For therapy, as determined by physician.
CHĒL-IRON PLUS TABLETS Bottles of 100	1 tablet t.i.d.

*Franklin, M., et al.: Chelate Iron Therapy, J.A.M.A. 166:1685, Apr. 5, 1958.
†U. S. Pat. 2,575,611

Kinney® KINNEY & COMPANY, INC. COLUMBUS, INDIANA



Greater comfort for postoperative and postpartum patients

abdominal distention and urinary retention
can often be prevented or promptly relieved
– with less need for uncomfortable enemas and catheters

Urecholine.

Chloride
(Bethanechol Chloride)

'Urecholine' helps restore normal function after surgery and childbirth by increasing the muscular tone of the gastrointestinal and urinary tracts. Postoperative "gas" pains can frequently be prevented or promptly relieved—with less need for uncomfortable enemas, intubation, and suction apparatus. Micturition is facilitated—without the discomfort and risk of infection inherent in catheterization.

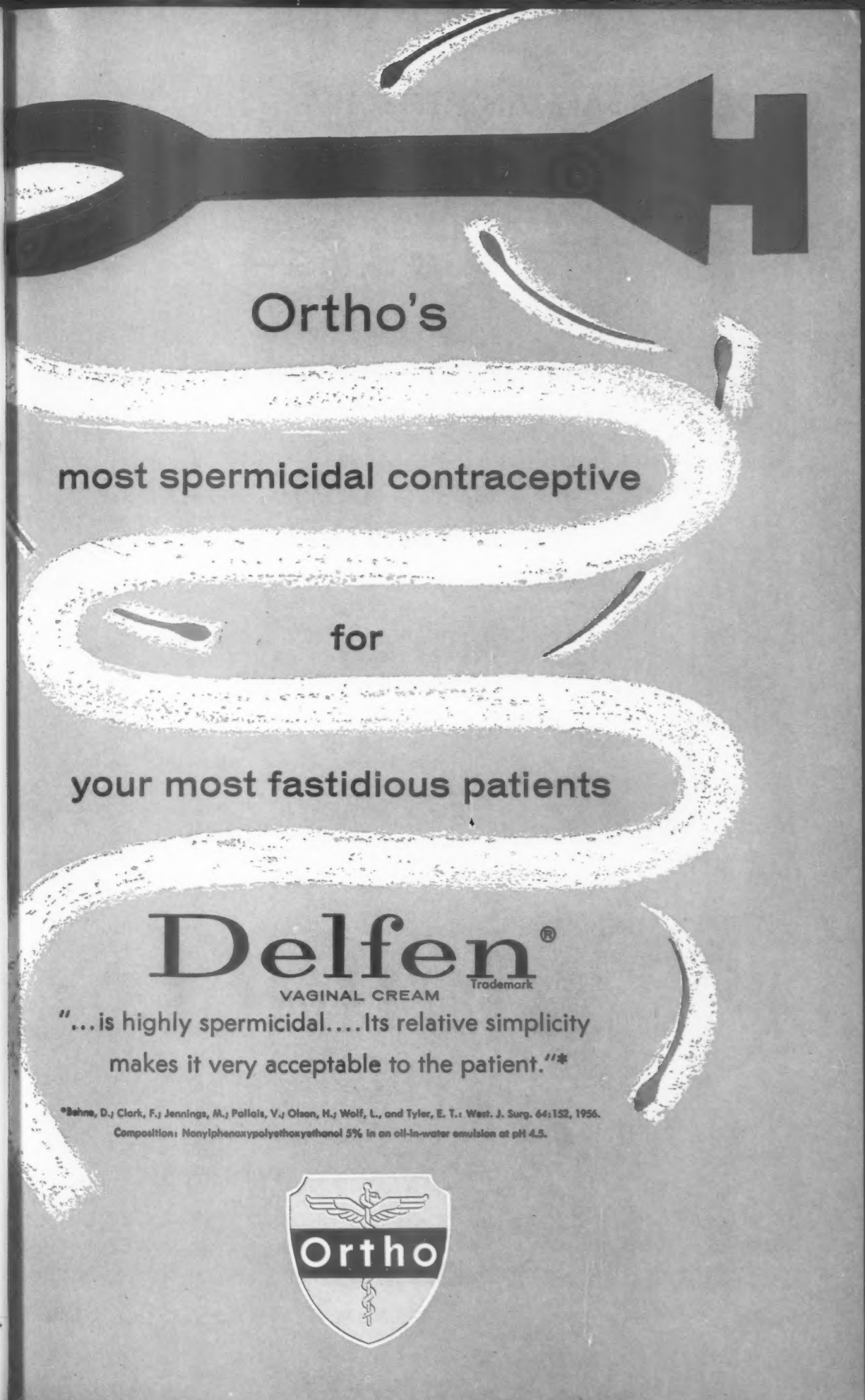
Administration and dosage: may be given prophylactically or therapeutically after surgery or childbirth. Usual oral dosage: 10 to 30 mg. three or four times daily. Usual subcutaneous dosage: 5 mg. three or four times daily.

Other indications: gastric atony and retention following vagotomy and other surgical procedures; chronic functional urinary retention due to atony without obstruction; megacolon, including congenital megacolon (Hirschsprung's disease); certain cases of paralytic ileus; to counteract side effects of antihypertensive ganglionic blocking drugs.

Supplied: 5 mg. and 10 mg. tablets, bottles of 100;
1-cc. ampuls containing 5 mg.

Urecholine is a trade-mark of MERCK & CO., INC.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.


Ortho's
most spermicidal contraceptive
for
your most fastidious patients
Delfen®
Trademark
VAGINAL CREAM
"...is highly spermicidal....Its relative simplicity
makes it very acceptable to the patient."*
*Behne, D.; Clark, F.; Jennings, M.; Pollais, V.; Olson, H.; Wolf, L., and Tyler, E. T.: West. J. Surg. 64:152, 1956.
Composition: Nonylphenoxypolyethoxyethanol 5% in an oil-in-water emulsion at pH 4.5.
Ortho

NOTABLY SAFE AND EFFECTIVE INHALATION ANALGESIA

"Trilene"®

Brand of trichloroethylene U.S.P. (Blue)

SELF-ADMINISTERED WITH THE "Duke"® University Inhaler

No. 3160 Model-M

With the "Duke" University Inhaler, "Trilene" analgesia can be self-administered by the patient, adult or child, under medical supervision, with a relatively wide margin of safety. Induction of analgesia is usually smooth and rapid. Inhalation is automatically interrupted if unconsciousness occurs. Outpatients can generally leave the doctor's office or hospital within 15 to 20 minutes.

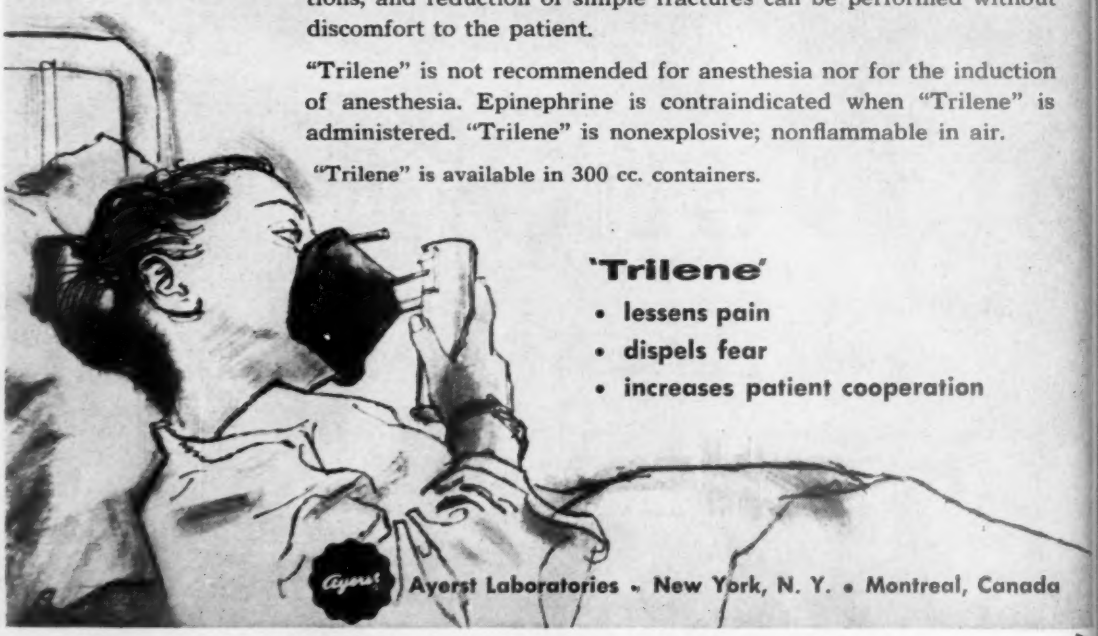
In Obstetrics . . . Self-administered "Trilene" will usually give effective relief of pain throughout labor and, for delivery, it may be employed in association with pudendal block or low spinal anesthesia.

In Pediatrics . . . The "Duke" University Inhaler is so easy to operate that even a child can administer his own "Trilene" analgesia.

In Surgery . . . With "Trilene," self-administered, many so-called "minor" yet painful procedures such as biopsies, suturing of lacerations, and reduction of simple fractures can be performed without discomfort to the patient.

"Trilene" is not recommended for anesthesia nor for the induction of anesthesia. Epinephrine is contraindicated when "Trilene" is administered. "Trilene" is nonexplosive; nonflammable in air.

"Trilene" is available in 300 cc. containers.



'Trilene'

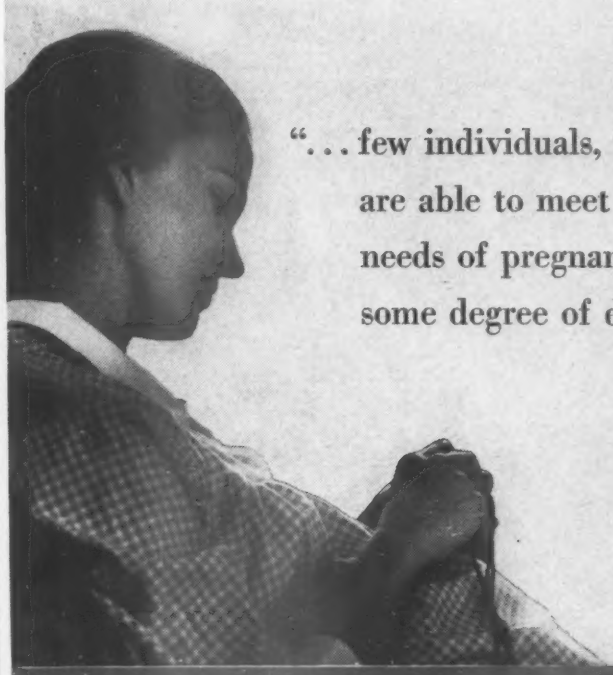
- lessens pain
- dispels fear
- increases patient cooperation

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

Ayerst Laboratories make "Trilene" available in the United States by arrangement with Imperial Chemical Industries Limited.

5717

June,



"... few individuals, if any, are able to meet the increased needs of pregnancy without suffering some degree of deprivation."[1]

Help assure your patients nutritionally perfect pregnancies

prescribe

Engran

Squibb Vitamin and Mineral Supplement

just 1 small capsule-shaped tablet daily

Each small capsule-shaped tablet provides:

Vitamin A	5,000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Vitamin K (as menadione)	0.5 mg.
Thiamine Mononitrate	3 mg.
Riboflavin	3 mg.
Pyridoxine HCl	2 mg.
Vitamin B_{12} Activity Concentrate	2 mcg.
Folic Acid	0.25 mg.
Niacinamide	20 mg.
Calcium Pantothenate	5 mg.
Ascorbic Acid	75 mg.
Calcium, elemental (as calcium carbonate, 375 mg.)	150 mg.
Iron, elemental (as ferrous sulfate exsiccated, 33.5 mg.)	10 mg.
Iodine, elemental (as potassium iodide, 0.2 mg.)	0.15 mg.
Potassium (as the sulfate)	5 mg.
Copper (as the sulfate)	1 mg.
Magnesium (as the oxide)	6 mg.
Manganese (as the sulfate)	1 mg.
Zinc (as the sulfate)	1.5 mg.

Supply

Bottles of 100 and 1000. For your patient's convenience, *Engran Term-Pak* provides 250 tablets – enough to last until term—in a handsome reusable glass jar plus a purse-size dispenser.

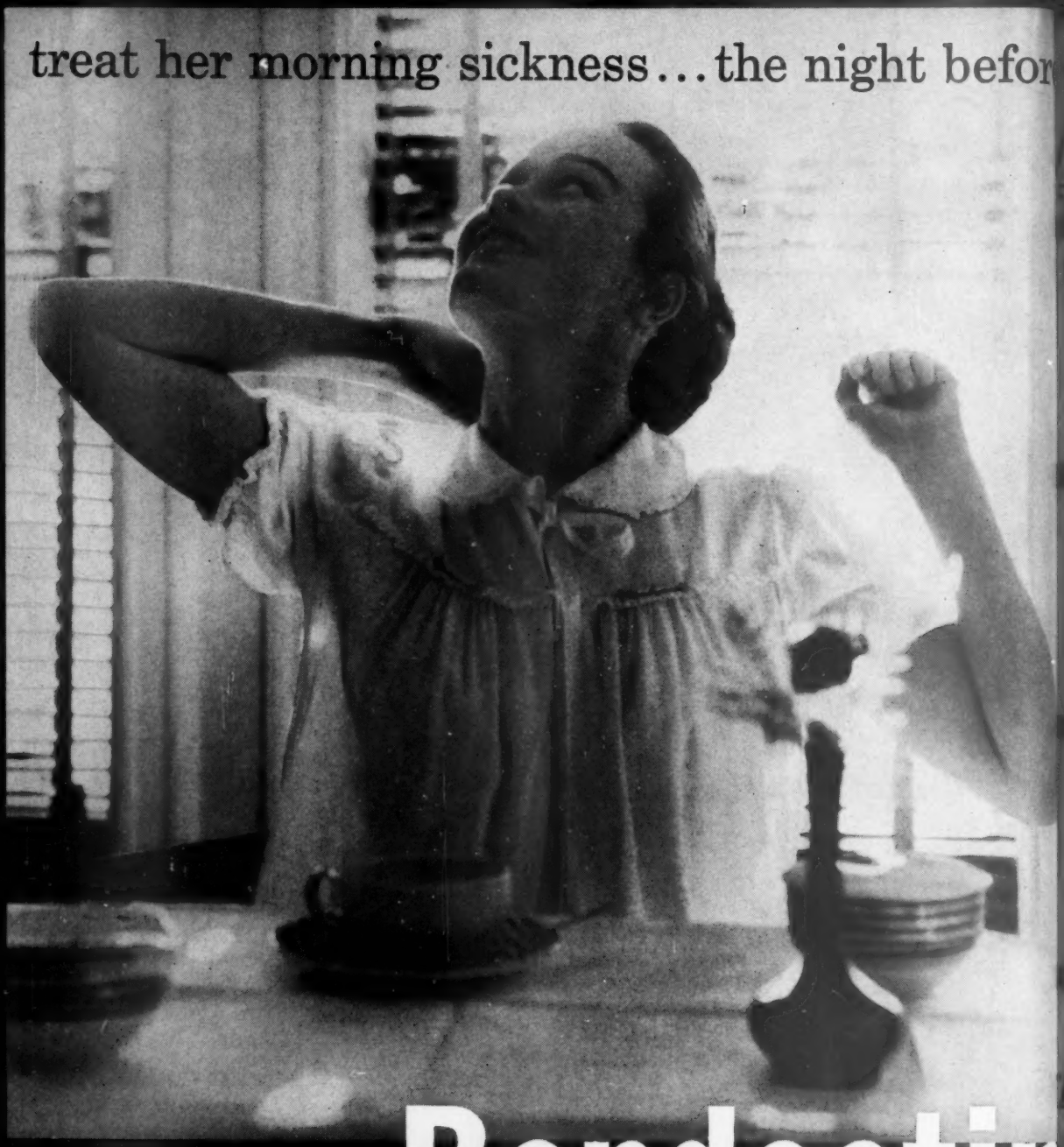
Reference: 1. Tompkins, W. T. in Wohl, M. G. and Goodhart, R. S.: *Modern Nutrition in Health and Disease*, Lea & Febiger, Philadelphia, 1955, p. 806.

Advantages

- specifically formulated for the mother-to-be
- generous amounts of 11 vitamins and 8 minerals
- contains vitamins A, C, D, K and the B complex
- provides phosphorus-free calcium, plus iron and trace elements

SQUIBB

Squibb Quality—the Priceless Ingredient



in 941 cases[1,2] effective in all but 17

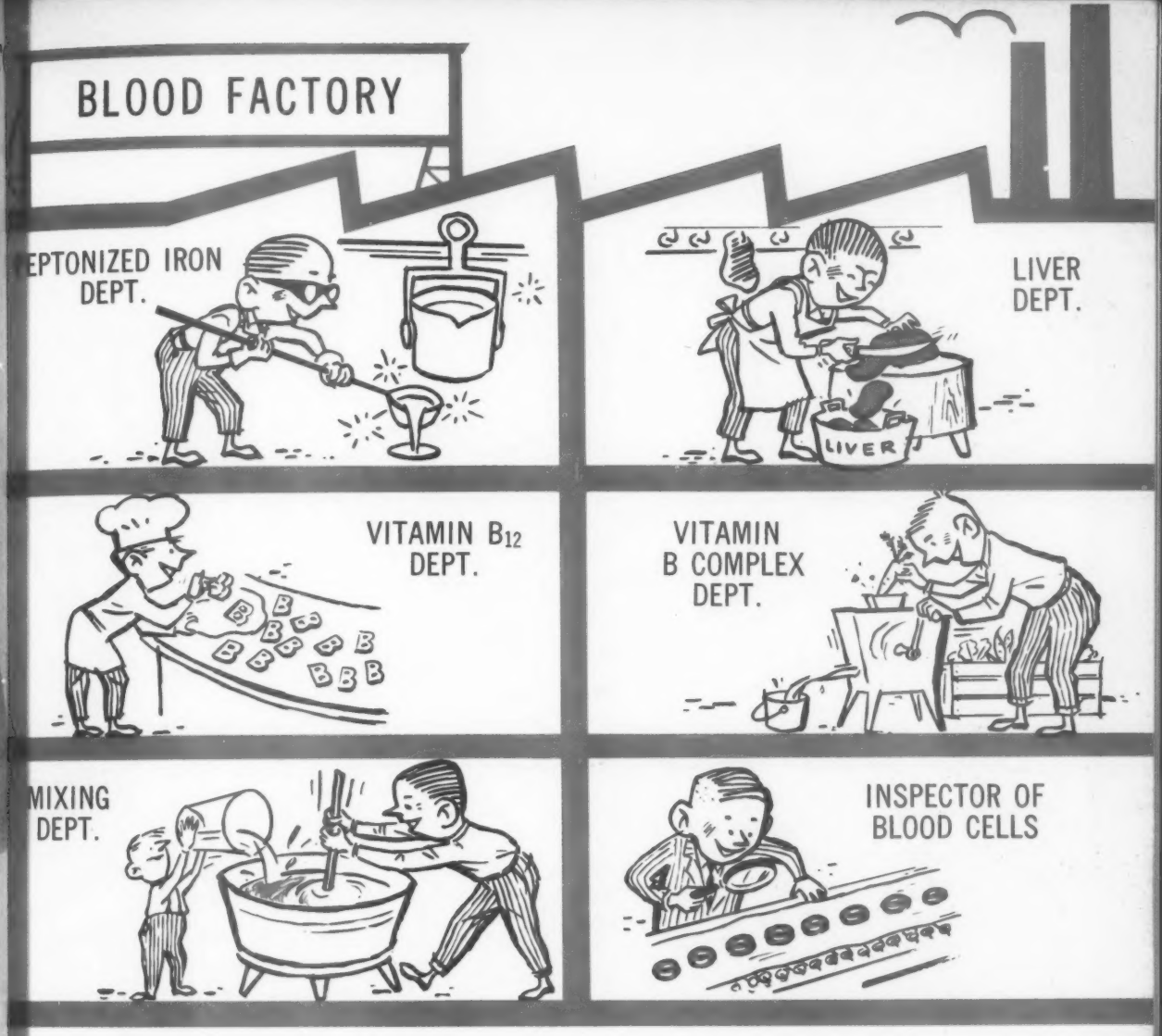
Bendectin

2 tabs h. s.

Merrell
SINCE 1828

THE WM. S. MERRELL COMPANY
New York • CINCINNATI • St. Thomas, Ontario
Another Exclusive Product of Original Merrell Research

1. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.
2. Clinical communications, 1956-57.



The preferred hematinic with **PEPTONIZED** *iron*

LIVITAMIN®

ptonized iron is virtually predigested. It is sorbed as well as ferrous sulfate, and is one-nth as irritating to the gastric mucosa. hemias refractory to other forms of iron will ten respond promptly to Livitamin therapy. The Livitamin formula, containing the B mplex, provides integrated therapy to cor-ct the blood picture, and to improve appetite d digestion.

Each fluidounce contains:

Iron peptonized	420 mg.
(Equiv. in elemental iron to	71 mg.)
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

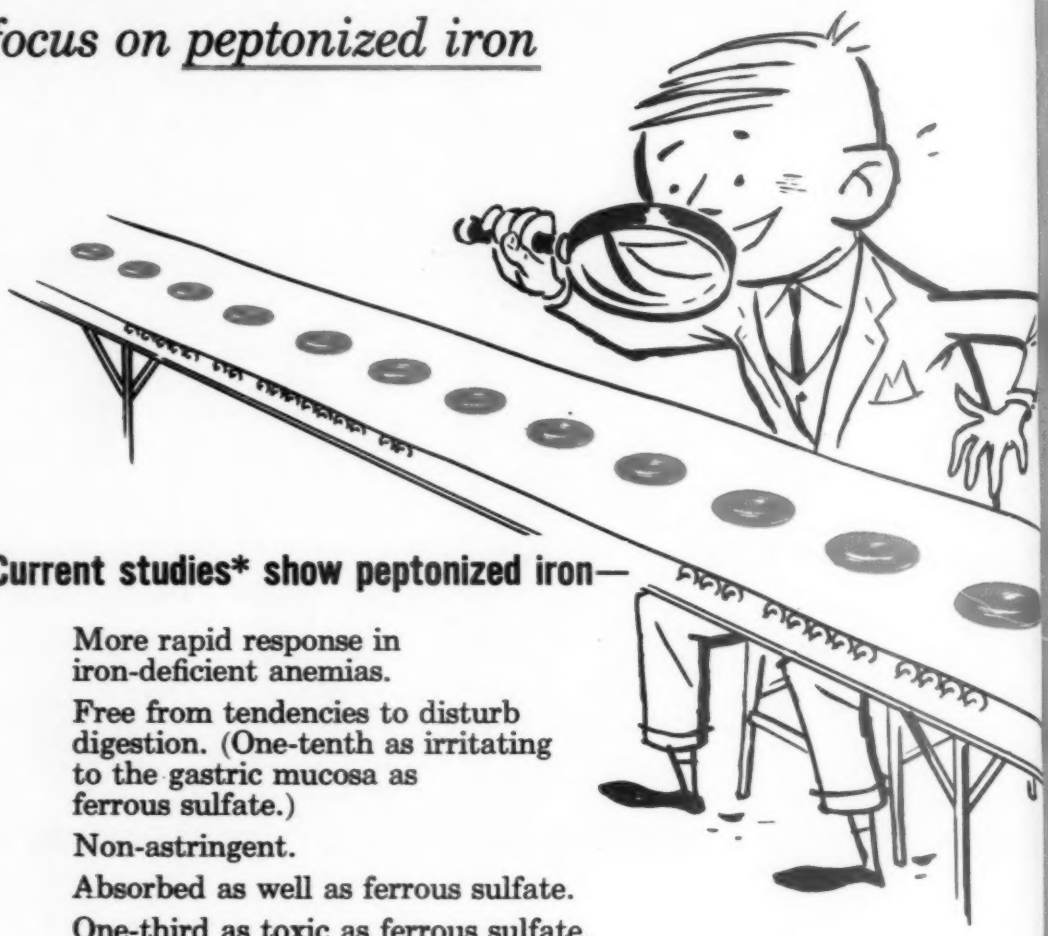
he S. E. MASSENGILL Company

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

For predictable therapeutic advantages . . .

focus on peptonized iron



Current studies* show peptonized iron—

More rapid response in iron-deficient anemias.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

Non-astringent.

Absorbed as well as ferrous sulfate.

One-third as toxic as ferrous sulfate.

LIVITAMIN® with Peptonized

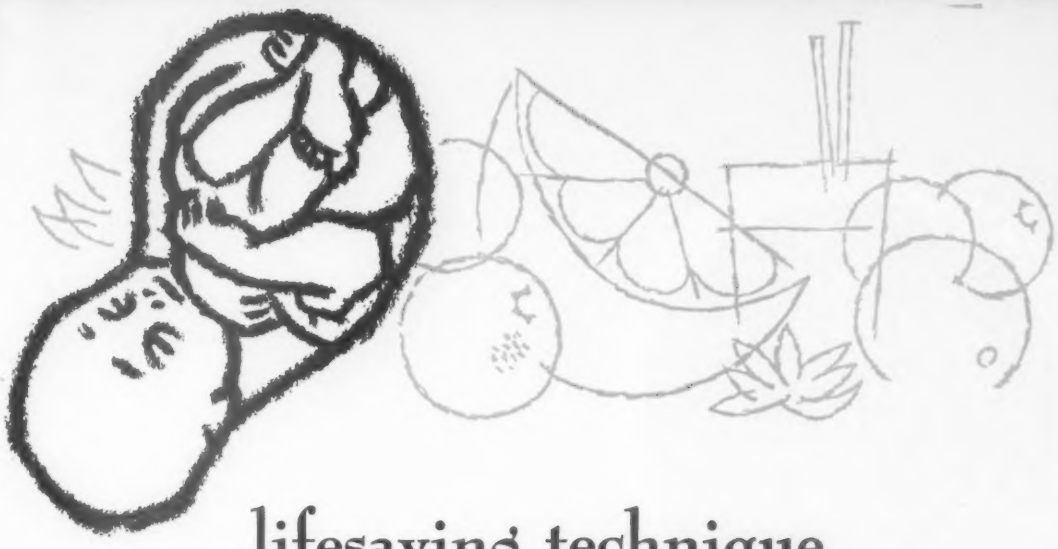
*Currently, mailings w
forwarded only at your r
Write for samples and
ture.*

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

The S. E. MASSENGILL Company

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRA



lifesaving technique for the unborn *includes* high citrus intake

Abortion-prone mothers deliver live babies in nearly 9 out of 10 pregnancies

Reporting on 134 pregnancies in 100 habitual abortion patients, Javert* describes a management program that resulted in live deliveries in all but 16 pregnancies. The previous 95.2 per cent rate of spontaneous abortions was reduced to 11.9 per cent by his comprehensive regimen which includes a high citrus intake (supplying up to 350 mg. of vitamin C daily), supplemented by 150 mg. of ascorbic acid and 5 mg. of vitamin K daily. Javert believes these antihemorrhagic vitamins "serve as a 'never-leak' . . . keeping physiologic decidual hemorrhage from becoming pathologic."

AVERAGE CITRUS INTAKE TO SUPPLY 350 MG. VITAMIN C DAILY

28 oz. orange or grapefruit juice	**or**	1 grapefruit 2 oranges 2 tangerines	**or**	½ grapefruit 1 orange 16 oz. orange juice

Florida Citrus Commission, *Lakeland, Florida*

*Javert, C. T.: Obst. & Gynec. 3:420, 1954; *Cf.* Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

for vaginitis caused

monilia,

trichomonads

or both

new specific

moniliacide MICOFUR™ and
brand of nifuroxime

he established specific

richomonacide FUROXONE®
brand of furazolidone

IMPROVED

TRICOFURON®

VAGINAL SUPPOSITORIES AND POWDER

RAPID RELIEF OF BURNING AND ITCHING OFTEN WITHIN 24 HOURS

ELIMINATES MALODOR ■ ESTHETICALLY ACCEPTABLE, NON-IRRITATING

% CLINICAL CURES* In 219 patients with either trichomonal vaginitis, nilial vaginitis, or both, clinical cures were secured in 187.

% CULTURAL CURES* 157 patients showed negative culture tests at 3 nths' follow-up examinations.

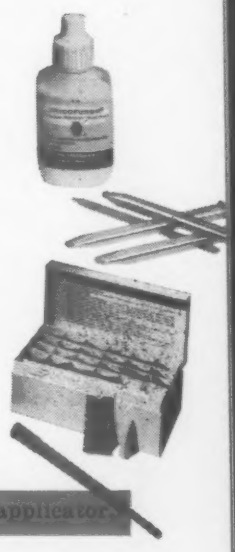
mple two-step treatment swiftly brings relief and trol of vaginal moniliasis and trichomoniasis.

EP 1 *Office* administration of TRICOFURON VAGINAL POWDER IMPROVED plied by the physician at least once a week, except during menstruation.

cofur 0.5% [*anti* 5-nitro-2-furaldoxime], the new nitrofuran fungicide, and Furoxone % in an acidic, water-soluble powder base). Plastic insufflator of 15 Gm., with 3 tary disposable tips. Also glass bottle of 30 Gm.

EP 2 Continued *home* use to maintain moniliacidal-trichomonacidal ion: TRICOFURON VAGINAL SUPPOSITORIES IMPROVED Employed by the ient each morning and night the first week and each night thereafter—ough one cycle, especially during the important menstrual days.

cofur 0.375% and Furoxone 0.25% in a water-soluble base).



EW: Box of 24 bullet-shaped suppositories, each hermetically sealed in green foil, with applicator.

of 12 wedge-shaped suppositories without applicator.

ined results of 12 clinical investigators. Data available on request.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

* T-C JAWS

another development by SKLAR

* *Sklar Needle Holders incorporate Tungsten Carbide (T-C) as an integral part of the jaws. This revolutionary development eliminates the many disadvantages of welded inserts.*

NEEDLE HOLDERS WITH TC-JAWS
(Pat. Appl'd. for)

Crile
Baumgartner
New Orleans
Mayo 6"—7"—8"
Masson
Sarot
Collier
Heuney

Stainless Steel

T-C Jaws Assure....

POSITIVE GRIP . . . The extremely hard surface and extra fine serrations prevent rotation of suture needles without indenting the surface.

DEPENDABILITY . . . No inserts to loosen or fall out . . . original temper and strength of jaws is preserved.

To distinguish T-C Needle Holders from the standard instruments, the handles are copper plated for ready identification.

These superior and dependable instruments are priced slightly higher than our standard pattern Needle Holders.

Available through accredited surgical supply distributors

Sklar LONG ISLAND CITY, NEW YORK

Preoperative sedation

for surgical and obstetrical patients

without

depression

of

vital

functions

EQUANIL® Meprobamate, Wyeth
PHENERGAN HCl Promethazine HCl, Wyeth
SPARINE® HCl Promazine HCl, Wyeth

A Wyeth tranquilizing drug for nearly every patient under stress

- Reduces preoperative apprehension and fear reactions to hospital environment
- Induces light sleep with easy awakening
- Facilitates cooperation and manageability prior to induction of anesthesia
- Promotes smoother, quieter emergence from anesthesia —controls postoperative excitement
- Prevents postoperative nausea and vomiting
- Relieves existing nausea and vomiting
- Diminishes dosage requirements for narcotics, analgesics, and sedatives

Comprehensive literature supplied on request

PHENERGAN®

HYDROCHLORIDE

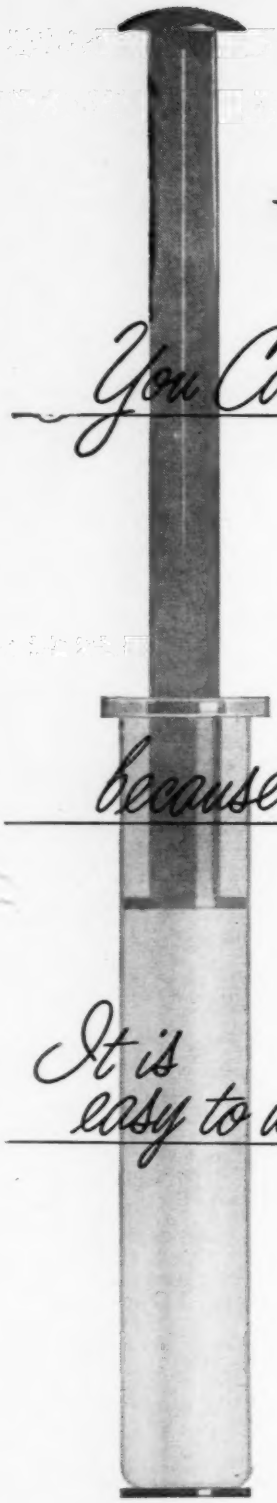
Promethazine Hydrochloride, Wyeth

INJECTION · TABLETS · SYRUP · SUPPOSITORIES

Wyeth

Philadelphia 1, Pa.

increasing monilial vaginitis
demands faster,
more specific therapy



You Can

STOP vulvar itching and burning faster

GET quicker cures . . .

with

gentia·jel®

the true specific for monilial vaginitis

because

Gentia-jel provides an unsurpassed monilial killing gel which disperses completely over the vaginal and cervical mucosa . . . penetrates into all folds . . . and bathes the vulvar labia. This soothing fungus and bacteria destroying gel provides fast gratifying relief of vulvar itching and burning, and results in quicker cures.

It is easy to use

Have the patient follow these simple steps: (1) Insert applicator and instill Gentia-jel on retiring. (2) Remove and discard applicator, place a pledget of cotton in the introitus and wear a perineal pad.

Supplied
In packages of 12 single-dose disposable applicators.

Westwood Pharmaceuticals
Division of Foster-Milburn Co. · Buffalo 13, New York

in infertility:

MALE—"In our experience we have found that the most effective hormone for use in male infertility is liothyronine ['Cytomel'] . . ."

Reed, D.C.; Browning, W.H., and O'Donnell, H.F.: Male Infertility: Diagnosis and Treatment; Scientific Section of Clinical Session of A.M.A., Philadelphia, December 3-6, 1957.

FEMALE—"As to the use of 'Cytomel' in the case of the infertile female, a definite place has been found for this drug . . . mainly [in] . . . women who have poor ovulation patterns . . ."

Queries and Minor Notes, J.A.M.A. *165*:1223 (Nov. 2) 1957.

℞ **Cytomel***

5 mcg. & 25 mcg. (scored) tablets

Smith Kline & French Laboratories, Philadelphia

★T.M. Reg. U.S. Pat. Off. for liothyronine, S.K.F. (L-triiodothyronine or LT3)

S-M-A expan

for the baby

S-M-A® FOOD FORMULA FOR INFANTS, WYETH

CONCENTRATED LIQUID • INSTANT POWDER

S-M-A protein is in physiologic proportion. The infant fed S-M-A receives a daily protein intake comparable to that of the breast-fed infant.

S-M-A fat is high in essential fatty acids. S-M-A supplies 20 calories per ounce, the same as human milk.

S-M-A provides *physiological* carbohydrate in the form of lactose in an amount (7%) closely adjusted to the average quantity in human milk.

S-M-A supplies vitamins and minerals in amounts adequate to meet the recognized needs of health and growth.

PHYSICIANS' COUNCIL FOR INFANT AND CHILD NUTRITION

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health

S-M-A for sound infant nutrition . . .

Wyeth

Philadelphia

an our baby-care resources

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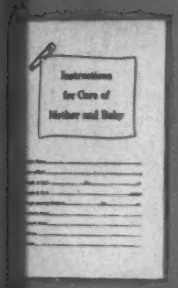

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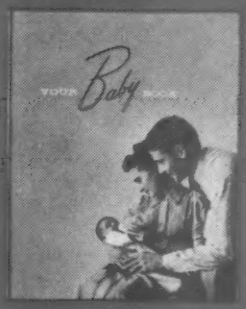

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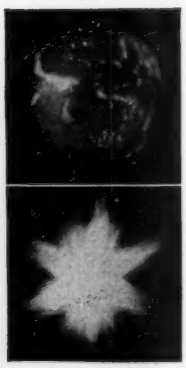

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References: 1. Weiner, H. H.: Clin. Med. *5*:25 (Jan.) 1958. 2. Decker, A.: New York J. Med. *57*:2237 (July 1) 1957. 3. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955.

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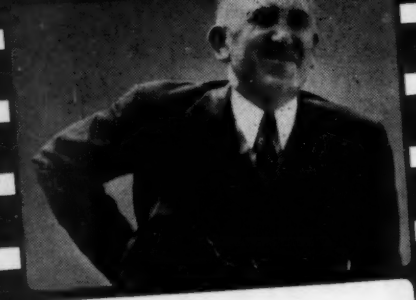

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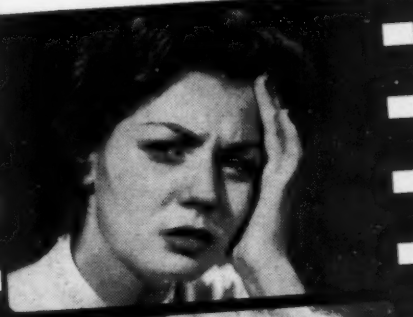

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References: 1. Woodhull, R. B.: Obst. & Gynec. 3:201, 1954. 2. Ausman, D. C.: Wisc. M. J. 53:322, 1954. 3. Edwards, B. E.: J. Indiana M. A. 47:869, 1954. 4. Ivory, H. S.: J. M. Soc. New Jersey 51:273, 1954.

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1. Birnberg, C.H., and Abitbol, M.M.: Obst. & Gynec. *10*:366, 1957.

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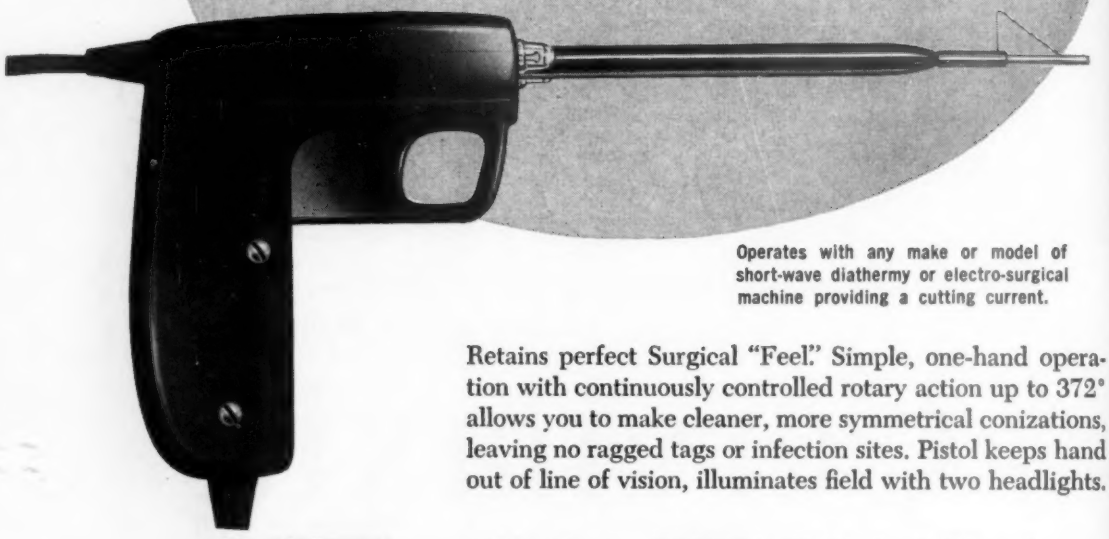

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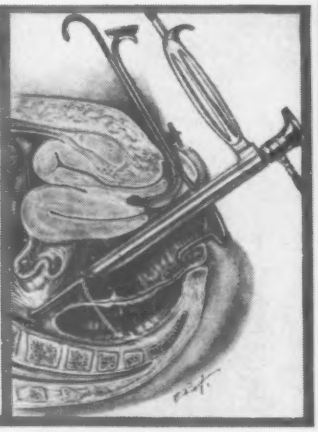

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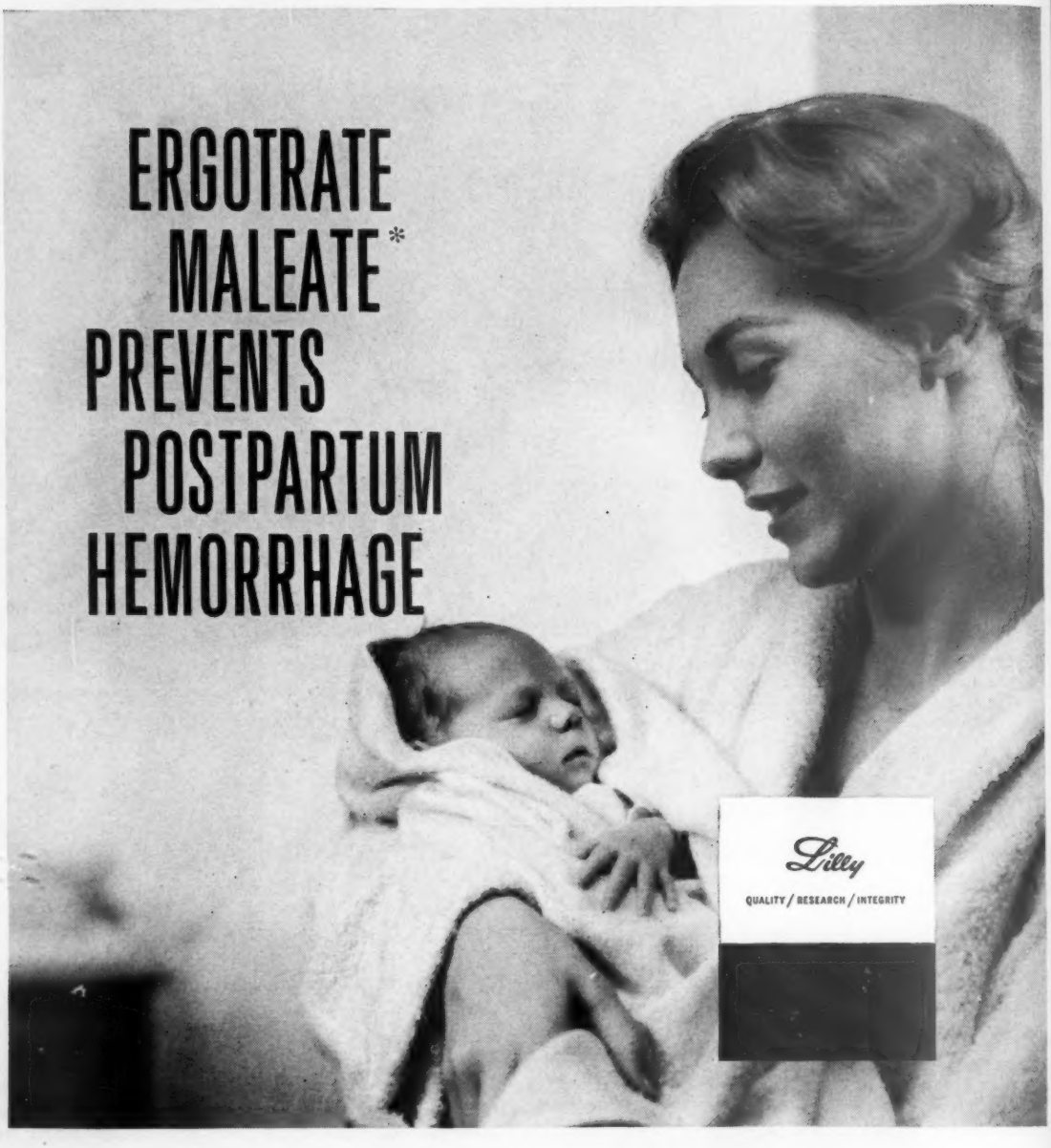

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Vol. 75, No. 6
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American Journal of

OBSTETRICS AND GYNECOLOGY

Obstetrics

THE EVALUATION OF TESTS TO DIFFERENTIATE PRE-ECLAMPSIA FROM HYPERTENSIVE DISEASE*

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IN "TOXEMIC" patients first seen in late pregnancy, the differential diagnosis is often difficult if the history is unknown. For this reason, various tests have been proposed for the separation of pre-eclampsia from hypertensive disease and from renal disease. In general, the author of such a test has been able to differentiate the "toxemias" in dissimilar groups and other investigators have confirmed the differentiation. In general, such studies have been concerned with a single one of the several proposed tests, although Govan, Mukherjee, Hewitt, and Harper[16] used three in conjunction (measurement of serum gonadotrophin levels, blood pressure response to tetraethylammonium bromide, and diuresis following a small water load).

The present report deals with the results found in a battery of five tests used successively in patients in whom the clinical diagnosis seemed fairly certain. The purpose was not so much to test the patients as to test the tests. The order in which the tests were done was as follows.

The cold pressor test was done first. Vasomotor instability, as shown by labile blood pressure, is almost generally considered to be characteristic of early and possibly of latent essential hypertension. Emotional stimuli, in hypertensive or prehypertensive subjects, often elicit marked rises in blood pressure.

*Supported by a research grant, H-1837, from the National Institutes of Health, Public Health Service.

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Several tests have been devised in which the stimulus is more or less standardized. Perhaps the most popular of these has been the cold pressor test of Hines and Brown,[17] in which the response of the blood pressure is measured during and after the immersion of one hand in ice water. These authors wrote that early hypertensive or prehypertensive subjects give exaggerated blood pressure rises in the test. Several investigators have applied the test in pregnancy, usually in an effort to predict the later development of toxemia. Reid and Teel[20] and Chesley and Chesley[8] found variable responses in repeated tests in the same patients and concluded that the test had no value in predicting the development of toxemia. Randall, Murray, and Mussey,[19] Briggs and Oerting,[5] and Krieger and Weiden[18] thought that the test did pick out patients likely to develop toxemia. As for the differentiation of hypertensive disease from pre-eclampsia, in patients with toxemia, Reid and Teel[20] did not find that the test had any practical value. Dieckmann, Michel, and Woodruff[13] found exaggerated responses to the test in pregnant women with hypertensive disease, while pre-eclamptic and eclamptic women showed only small rises in blood pressure. Bak[4] found minimal responses to the test during pre-eclampsia and Assali and Prystowsky[3] found that pre-eclamptic patients reacted no differently from normal pregnant women.

The second test used was the response of the blood pressure to vasopressin. Dieckmann and Michel[12] and Schockaert and Lambillon[22] found that women with pre-eclampsia are especially sensitive to posterior pituitary extract, or its pressor principle. A dose of vasopressin that elicited only a negligible blood pressure rise in normal pregnant women similarly caused almost no reaction in pregnant women with hypertensive disease. In contrast, similar doses given to women with pre-eclampsia elicited marked rises in blood pressure, decreases in urine volume output, and subjective reactions. de Valera and Kellar[10] made similar observations, but found that the variability of response vitiated its differential diagnostic value. Browne[6] reported that pre-eclamptic women who had given normal responses in early pregnancy showed the sensitivity during toxemia and lost it in the puerperium.

The third test used was the response of the blood pressure to intravenous tetraethylammonium chloride (TEAC). Assali[1] and Assali, Brust, Garber, and Ferris[2] reported that normal pregnant women responded to intravenous TEAC with marked drops in blood pressure, even to shock levels. Pregnant women with hypertensive disease reacted in a similar manner. Women with pre-eclampsia, however, showed negligible drops, or even increases. Dumoulin[15] and Govan, Mukherjee, Hewitt, and Harper[16] confirmed these findings, except that the former noted that some patients with mild pre-eclampsia had marked falls in blood pressure and the latter group found that some of their patients with essential hypertension did not. Werkö and Brody[24] often found marked decreases in the blood pressure of women with the diagnosis of pre-eclampsia.

The fourth test used was the sodium tolerance test, described by Dieckmann, Pottinger, and Rynkiewicz.[14] They infused a liter of 2.5 per cent sodium chloride within a 30 minute period, emptied the bladder 15 minutes after the

infusion and then collected two 1-hour urine specimens. In 20 women with pre-eclampsia, the mean urinary sodium concentration was 101 mEq. per liter, with a standard deviation of 65. In 28 pregnant women with hypertensive disease, the mean urinary sodium was 196 with a standard deviation of 52 mEq. per liter. In normal pregnant women sodium was concentrated to an average of 240 mEq. per liter (standard deviation of 40). Willson, Williams, and Hayashi[25] used this test on a large number of women and, in general, confirmed these findings and also found that hypertensive women with superimposed pre-eclampsia and "pre-pre-eclampsia" showed the pattern of pre-eclamptic response. They wrote: "There is, however, overlapping of the values for sodium excretion between those with pre-eclampsia and those in the other groups so that the salt test cannot be utilized alone to establish a diagnosis." Actually, this conclusion is implicit in the standard deviations reported by Dieckmann, Pottinger, and Rynkiewicz.[14] They had set the urinary sodium concentrations to be used in differential diagnosis as less than 144 mEq. per liter for pre-eclampsia; this cut-off point represents their mean plus 0.67σ. In a normal distribution, 25 per cent of their pre-eclamptic patients might be expected to concentrate sodium to more than the limiting 144 mEq. per liter, and, similarly, 16 per cent of their hypertensive patients might be expected to fall below their dividing line.

The fifth test used was the renal clearance of urate. Chesley and Williams,[9] with confirmation by Seitchik,[23] found that in pre-eclampsia the renal tubules reabsorb more than the usual fraction of urate filtered by the glomeruli. The urate clearance is depressed in pre-eclampsia, both by the characteristic reduction in glomerular filtrate rate (inulin clearance) and by the increased tubular reabsorption. Chesley[7] later reported upon a large series of patients in whom the simultaneous clearances of urea and urate were measured (the urea clearance roughly parallels the rate of glomerular filtration). In normal pregnant women and in pregnant women with uncomplicated hypertensive disease, the two clearances were about equal in terms of percentages of average normal. In renal disease, both clearances were depressed, with the urea clearance usually showing the greater reduction. In pre-eclampsia, the urea clearance was moderately and the urate clearance markedly depressed. The characteristic findings of pre-eclampsia were seen in hypertensive women who had superimposed pre-eclampsia. Chesley[7] reported, however, that there was considerable overlapping of the clearances, from group to group. For instance, the ratio, urate clearance/urea clearance (in terms of percentages of average normal), was greater than 0.65 in 17.8 per cent of the women thought to have pre-eclampsia, while 10 per cent of normal pregnant women and about 15 per cent of those with uncomplicated hypertensive disease fell below this ratio.

Material and Methods

The patients used were carefully selected on the basis of clinical evidence for the diagnosis of pre-eclampsia or hypertensive disease. Fifteen patients

were thought to have pre-eclampsia; 12 were primigravidas and the 3 multigravidas were known to have been normal in their previous pregnancies. All 15 had been clinically normal until the onset of hypertension, edema, and proteinuria late in pregnancy.

The 16 women thought to have uncomplicated hypertensive disease included 11 multiparas, all with histories of previous "toxemia" and hypertension either before or early in pregnancy. Of the 5 primigravidas, 3 gave a history of prepregnancy hypertension and all had hypertensive blood pressure recordings before midpregnancy. None had any clinical evidence of superimposed preeclampsia.

All patients were in the hospital, at bed rest much of the time. The blood pressure was checked repeatedly over a period of at least half an hour and when a steady level had been attained, the tests were begun (usually in the afternoon). In the cold pressor test, the hand was immersed in ice water, up over the wrist, for 1 minute. The blood pressure was measured midway and at the end of the minute and at intervals of 1 to 2 minutes until it had returned to the original level. One minim of Pitressin was then injected subcutaneously and the blood pressure measured every 2 minutes for at least 10 minutes, or until it had returned to the basal level if the rise were prolonged. When it had been established that the blood pressure was steady, at or near the original level, 4 ml. of Etamon* (400 mg. of TEAC) was injected intravenously and the blood pressure followed until it had returned to the original level. In the first 5 minutes, readings were taken at intervals of ½ to 1 minute.

On the following morning, 830 ml. of 3 per cent sodium chloride was infused in a period of 20 to 30 minutes (a slight modification from the 1,000 ml. of 2.5 per cent saline used by Dieckmann, Pottinger, and Rynkiewicz[14]). The bladder was emptied 5 to 15 minutes after the end of the infusion and the urine output collected at intervals thereafter. In about half the cases, the procedure was more elaborate, as follows: At about 9 A.M. a multiple-eyed catheter was inserted into the bladder and a constant infusion of 1 per cent inulin in 5 per cent dextrose was started and given at the rate of 3.7 ml. per minute. As soon as this infusion was started, 3 Gm. of inulin, in 10 per cent solution, was injected through the infusion tubing. After about 45 minutes, the bladder was drained, washed out with 20 ml. of distilled water, and blown out with 50 c.c. of air. All subsequent urine collections were made in the same manner. Venous blood samples were taken midway between the urine collections. The inulin and urate clearances were measured during 3 control periods before the hypertonic saline infusion was given. Sodium concentrations in the urine were corrected for the dilution occasioned by washing out the bladder.

Inulin was measured by the resorcinol method of Roe, Epstein, and Goldstein.[21] Urate was measured by the photometric method described by Chesley.[7] Sodium analyses were done with a Perkin-Elmer 52C flame photometer, with an internal lithium standard.

Results

All of the basic data are recorded in Tables I and II.

Cold Pressor Test.—Hines and Brown[17] originally set the upper limit of blood pressure rise at 15 mm. Hg, but later increased this to 22 mm. Hg. We have followed Dieckmann[11] in using a rise of 29 mm. Hg as the dividing line between normal and abnormal response to the cold test.

*Parke, Davis & Company, Detroit, Mich.

TABLE I. RESULTS OF TESTS IN PATIENTS WITH CLINICAL DIAGNOSIS OF PRE-ECLAMPSIA
(Parentheses denote findings inconsistent with clinical diagnosis)

NO.	BLOOD PRESSURE CHANGES IN MM. HG*						URATE CLEARANCE (ML./MINUTE)	RATIO, URATE/INULIN CLEARANCES	URINE SODIUM CONCENTRATION (mEq./LITER
	COLD PRESSOR TEST		VASOPRESSIN TEST		TEAC TEST				
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC			
1	(63)	(31)	46	34	55	40	5.9	8.4	--
2	18	4	20	(12)	-6	-2	12.1	5.3	(168)
3	25	10	(13)	(10)	25	7	--	--	(176)
4	16	10	22	(4)	61	28	9.1	9.7	126
5	18	16	44	34	38	28	6.1	6.1	119
6	(40)	20	30	21	62	29	8.0	8.4	122
7	20	10	(0)	(-2)	(-36)	(-30)	8.8	(11.0)	70
8	15	20	38	18	-12	10	(14.1)	--	(213)
9	(44)	(34)	26	32	34	22	6.0	4.3	(155)
10	14	8	16	(8)	-14	-6	10.7	--	(161)
11	4	4	20	18	-4	-2	(17.6)	--	107
12	22	20	(10)	28	(-30)	-12	6.6	--	137
13	(30)	10	26	26	(-54)	(-52)	10.0	--	(153)
14	(45)	(34)	(-30)	(-5)	(-28)	-10	5.4	--	130
15	24	(34)	32	40	--	--	7.8	--	83
Mean	26	18	21	16	6	4	9.1	--	137
Median	22	16	22	18	-5	3	8.4	--	133
Standard deviation	15	11	18	12	37	24	3.4	--	36

*Blood pressure rises unless denoted as minus.

TABLE II. RESULTS OF TESTS IN PATIENTS WITH CLINICAL DIAGNOSIS OF HYPERTENSIVE DISEASE
(Parentheses denote findings inconsistent with clinical diagnosis)

NO.	BLOOD PRESSURE CHANGES IN MM. HG*						URATE CLEARANCE (ML./MINUTE)	RATIO, URATE/INULIN CLEARANCES	URINE SODIUM CONCENTRATION (mEq./LITER
	COLD PRESSOR TEST		VASOPRESSIN TEST		TEAC TEST				
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC			
1	50	44	12	6	-28	-20	15.3	11.4	228
2	50	(28)	(18)	12	-32	(-10)	(8.5)	(5.9)	347
3	(22)	(6)	(28)	10	(26)	(20)	13.4	10.3	155
4	30	(14)	-4	6	--	--	--	--	155
5	(11)	(18)	1	13	(16)	(18)	--	--	258
6	(26)	(17)	(28)	12	(38)	(37)	14.7	11.2	(62)
7	40	(26)	-10	-4	-42	(-10)	14.1	9.1	(134)
8	(14)	(12)	2	4	(54)	(44)	12.9	--	245
9	30	(24)	6	10	--	--	(9.0)	--	265
10	(14)	(20)	12	10	(-10)	(-14)	35.8	27.2	252
11	(12)	(4)	0	6	(22)	(10)	18.8	--	354
12	50	40	-4	4	(-10)	(0)	(6.6)	--	(123)
13	(26)	34	0	0	(-10)	(-4)	17.0	--	172
14	(18)	(7)	0	0	--	--	(9.6)	--	282
15	(22)	(14)	8	8	-40	-20	15.9	--	248
16	30	(18)	4	2	-30	-14	26.8	--	263
Mean	28	20	6	5	-4	2	15.6	--	221
Median	26	18	3	6	-10	-5	14.4	--	246
σ	13	11	11	6	29	22	7.4	--	78

*Blood pressure rises unless denoted as minus.

Six of the 15 pre-eclamptic women had abnormal reactions to the cold test in either systolic or diastolic rises, or in both (Table I). Fourteen of the hypertensive patients failed to show abnormal rises in blood pressure; 8 reacted normally in both systolic and diastolic and 6 had only normal rises in either the systolic or diastolic reading (Table II). If the differential diagnosis rested upon the cold pressor test alone, the clinical diagnosis of pre-eclampsia would have been wrong in 40 per cent and the clinical diagnosis of hypertensive disease wrong in 87.5 per cent of the cases.

The average increase in systolic pressure was 26 mm. Hg in the cases diagnosed as pre-eclampsia and 28 mm. Hg in the patients thought to have hypertensive disease. The mean rises in diastolic pressure were 18 and 20 mm. Hg, respectively. Obviously, these are not significant differences and the superfluous statistical analysis in Table III indicates this.

Therefore, we confirm Reid and Teel's[20] findings in concluding that the cold pressor test has no practical value in differentiating pre-eclampsia from hypertensive disease.

Vasopressin Test.—Dieckmann[11] set 15 mm. Hg as the dividing line between normal and abnormal rises in blood pressure following vasopressin injection. Table I shows that 7 of the 15 pre-eclamptic patients had lesser increases in either the systolic or diastolic blood pressure, or in both. Only 3 gave wholly normal responses (in both systolic and diastolic readings), however. Only 3 of the 16 hypertensive patients reacted with abnormal blood pressure rises and these responses were all in the systolic readings alone. Thus, if the differential test were based upon reactions in both systolic and diastolic pressures, the results of the test would agree with the clinical diagnosis in all 16 of the hypertensive women, but would disagree with the clinical diagnosis in 7 of the 15 pre-eclamptic patients.

In pre-eclampsia, the mean rise in systolic pressure was 21 mm. Hg and in diastolic, 16 mm. Hg. These responses are significantly different from the mean rises of 6 mm. Hg in systolic and 5 mm. Hg in diastolic pressures found in the hypertensive women, as the statistical analysis in Table III shows. Generalization from 31 cases would be hazardous, but it appears that de Valera and Kellar[10] were correct in concluding that this test is not specific enough to be used alone as a diagnostic test.

TEAC Test.—Assali and Prystowsky[3] found that the average decrease in blood pressure, in patients with pre-eclampsia, was 8 per cent in the systolic and 4 per cent in the diastolic readings; 6 of their 15 patients had increases in either systolic, diastolic, or both readings. In normal pregnancy, the fall in systolic pressure ranged from 13 to 64 per cent and averaged 36 per cent; the range of fall in the diastolic was from 6 to 62 per cent and the average was 37 per cent. Assali has written: "In essential hypertension associated with pregnancy the fall is usually comparable to [that in] normal pregnant patients."

Tables I and II include the blood pressure responses to TEAC. Four of the 15 pre-eclamptic patients had atypical drops of the degree seen in normal pregnancy or essential hypertension. Six of the 15 had blood pressure rises, exactly the same proportion as observed by Assali and Prystowsky.[3] The rises that they saw were not so marked, however. Exactly half of the patients thought to have essential hypertension failed to show significant blood pressure falls after intravenous TEAC.

The pre-eclamptic and hypertensive patients did not differ from each other in the average response to TEAC, as the statistical analysis in Table III shows.

Urate Clearance.—Chesley[7] found the urate clearance to average 16.8 ml. per minute in late normal pregnancy, 15.9 ml. per minute in pregnant women

with uncomplicated hypertensive disease, and 7.8 ml. per minute in women with pre-eclampsia. (The average for nonpregnant women was 15.0 ml. per minute, which was taken as 100 per cent.)

Table I shows that the urate clearance was depressed in 12 of the 14 pre-eclamptic patients in whom it was measured. Also, in Case 2, the clearance of 12.1 ml. per minute was well up in the range of normal. The glomerular filtration rate was markedly elevated, however, and the fraction of filtered urate that was excreted was less than half of normal. In the hypertensive group (Table II), the urate clearances were depressed in 4 of the 14 cases. Unfortunately and contrary to the recommendation of Chesley,[7] the simultaneous clearance of urea or inulin was not measured in 3 of these; in the other case, the findings were typical of pre-eclampsia in that an abnormal fraction of filtered urate was reabsorbed by the renal tubules.

The average urate clearance in patients thought to have pre-eclampsia was 9.1 ml. per minute, as contrasted to a mean of 15.6 in the hypertensive group. The difference is statistically significant (Table III). As in the much larger series studied by Chesley,[7] however, there is overlapping of the results from group to group. This test, alone, would not always give the correct diagnosis.

Sodium Tolerance Test.—Dieckmann, Pottinger, and Rynkiewicz[14] suggested that in pre-eclampsia urinary sodium is not concentrated to more than 144 mEq. per liter, while in hypertensive pregnant women higher levels are achieved. Six of the 14 patients thought to have pre-eclampsia did not conform to this criterion (Table I), while 3 of the 16 with hypertension fell within the range of pre-eclampsia.

The average urinary sodium concentration of 137 mEq. per liter in the women with pre-eclampsia is significantly lower than the mean of 221 observed in the pregnant women with hypertensive disease (Table III). As Willson, Williams, and Hayashi[25] concluded, however, the groups overlap in their responses and the salt test therefore is not specific.

TABLE III. COMPARISON OF PREGNANT WOMEN WITH PRE-ECLAMPSIA AND HYPERTENSION IN THEIR AVERAGE RESPONSES TO THE TESTS

	MEAN RISE IN BLOOD PRESSURE IN MM. HG							
	COLD PRESSOR TEST		VASOPRESSIN TEST		TEAC TEST		URATE CLEARANCE	URINE SODIUM CONCENTRATION
	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC		
Mean in pre-eclampsia	26	18	21	16	6	4	9.1	137
Mean in hypertension	28	20	6	5	−4	2	15.6	221
t	0.38	0.49	2.70	3.14	0.76	0.23	2.87	3.56
p	>0.5	>0.5	0.01	<0.01	>0.1	>0.5	<0.01	<0.01

Comment

The cold pressor test seems to be of no value in the differentiation of pre-eclampsia from hypertensive disease, either in the present small series or in the larger numbers of cases studied in the past. While 31 cases form a shaky basis for generalization, the TEAC test also seems to be of little practical value; this conclusion is buttressed by the findings of Dumoulin,[15] Govan, Mukherjee, Hewitt, and Harper,[16] and Werkö and Brody.[24]

None of the other three tests studied is specific and the results overlap from group to group for this reason. If we accept the clinical diagnosis as correct, the diagnostic error of the vasopressin test was 32 per cent (taking

account of any "atypical" change in either systolic or diastolic blood pressure). The diagnostic error of the urate clearance was about 20 per cent and of the sodium tolerance test, 30 per cent.

In 12 cases, all 3 tests were consistent with the clinical diagnosis and in 3 others, where only 2 tests were done, the 2 tests were also in agreement. Of the remaining 16 cases, 2 of the 3 tests agreed with the clinical diagnosis in 11, leaving 5 cases (about 16 per cent) in which 2 of the 3 tests gave results inconsistent with the clinical diagnosis (in 2 of the pre-eclamptic and 3 of the hypertensive patients). If we take the 3 tests in conjunction and regard agreement between any 2 as diagnostic, it turns out that the salt test gave the dissident answer in 6 instances, in 5 of which it also disagreed with the clinical diagnosis. The urate clearance was inconsistent with the results of the other 2 tests in 4 cases and in 3 of these it also disagreed with the clinical diagnosis. The vasopressin test gave the odd answer in 5 cases, in 3 of which it also was not consistent with the clinical diagnosis. It appears that no one of these tests is any better than either of the other two and even when used in conjunction they would carry a diagnostic error of nearly 20 per cent.

The average urate clearance and the average responses to the vasopressin and sodium tolerance tests were significantly different in the pre-eclamptic women from the results in the pregnant women with hypertensive disease. This might suggest that the findings in these tests reflect some basic physiopathologic features of pre-eclampsia and that the overlapping of the results, from group to group, arises from mistakes in clinical diagnosis. Against this interpretation is the fact that in individual cases the tests often point to contradictory diagnoses. As was noted above, one or another of the tests disagreed with the other two in 15 of the 27 patients studied with all 3 tests.

Willson, Williams, and Hayashi[25] reported that the salt test gave abnormal results in some women who later developed pre-eclampsia. Similarly, Chesley[7] found that the urate clearance was depressed in some "pre-pre-eclamptic" women. Could the responses typical of pre-eclampsia, found in women thought to have hypertensive disease, point to superimposition of pre-eclampsia not yet manifest? Seven of the 16 hypertensive pregnant women gave abnormal responses to at least one of the tests (Cases 2, 3, 6, 7, 9, 12, and 14 of Table II). In 4 the reaction to a single test was abnormal (urate clearance in 2, vasopressin and salt tests, 1 each). In the other 3, abnormal responses were found to 2 tests (1 to vasopressin and salt tests, 1 to vasopressin and urate clearance tests, and 1 to urate clearance and salt tests). In this welter there were 3 abnormal responses to vasopressin (all in systolic blood pressure alone), 4 depressed urate clearances, and 3 abnormally low urinary sodium concentrations. If these abnormal reactions were signs of incipient pre-eclampsia there must be no consistent pattern; it seems more probable that they were statistical variations from the means to be seen in hypertensive disease. Only 2 of these 7 patients were delivered within a week after the tests, while the others carried their pregnancies for periods up to 4 more weeks. None developed proteinuria or significant increases in blood pressure such as to justify the diagnosis of superimposed pre-eclampsia.

Summary and Conclusions

Thirty-one pregnant women were carefully selected on the basis of a fairly definite clinical diagnosis of either pre-eclampsia or hypertensive disease.

A battery of 5 tests that have been proposed for the differentiation of pre-eclampsia from hypertensive disease was studied in the 31 patients.

It is concluded that the blood pressure responses to the cold pressor test and to the intravenous injection of tetraethylammonium chloride were not significantly different in the two groups of patients. These two tests seem to have no practical value in the differential diagnosis.

The average responses of women with pre-eclampsia were significantly different from the average responses of pregnant hypertensive women in 3 of the tests studied.

In pre-eclampsia the mean rise in blood pressure after subcutaneous injection of vasopressin was greater than in hypertensive women. The responses overlapped from group to group, however.

In pre-eclampsia the mean renal clearance of urate is significantly depressed as compared to the mean clearance in pregnant hypertensive women. However, the clearances overlap from group to group.

In pre-eclampsia the mean urinary concentration of sodium, after salt loading, is significantly less than in pregnant hypertensive women. Again, there is considerable overlapping of the responses from group to group.

None of the tests is specific enough to be used for definite diagnosis. Using the 3 tests in conjunction does not improve the situation, for any one of the tests is equally likely to disagree with the other two (and with the clinical diagnosis).

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THE PLASMA ANTIDIURETIC ACTIVITY IN TOXEMIA OF PREGNANCY*

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THE knowledge of pituitary gland function in relation to pregnancy leaves much to be desired, and its role in toxemia is even less well understood. All three of the principal functions of the posterior pituitary might well find a place in explaining the etiology of toxemia, since this disorder is characterized by (1) hypertension of vasoconstrictive origin; (2) early violent labor which might be thought of as being induced by an increased blood level of posterior pituitary oxytocic hormone, and (3) water retention which might have its basis in increased amounts of circulating antidiuretic hormone. The present work concerns itself with the last of these three possibilities.

Previous work reported by Jones,[4] Dieckmann,[2] Heller,[3] and Anselmino[1] showed widely divergent results and emphasized the fact that no reliable method for the determination of available antidiuretic hormone has been devised. A number of the problems relative to the extraction and concentration of the hormones were recognized by Melville[7] in his attempts to show its presence in elevated amounts in toxemia. Levitt[5] and Theobald[9] used ultrafiltrates of plasma and concluded that aliquots of posterior pituitary hormone previously added to blood could not be extracted quantitatively. More recently, Teel and Reid[8] reported on a technique in which the urine of the toxemic patient was injected subcutaneously into hydrated albino rats, and the resulting rate of water excretion of the animal was then measured. This procedure demonstrated the presence of antidiuretic activity in the urine of the toxemic patients tested. In toxemia, however, a change in renal threshold may occur or the associated vasopressin may cause retention so that ADH activity in the urine does not reflect the actual plasma levels of this substance. In this regard the study of the urinary level of ADH does not differ from studies of the urinary levels of any other substance, i.e., no fundamental relationship exists between the amount or concentration of a substance appearing in the urine and its concentration or functional ability in the extracellular fluid.

In view of these considerations, a practical bioassay technique for the determination of antidiuretic activity in plasma has been applied to patients with toxemia of pregnancy.

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Method

Following the method previously outlined,[6] albino rats were placed in metabolism cages and urinary excretion recorded. In an effort to minimize individual animal variations, 4 animals were used for each determination. The rats were weighed and then hydrated by the introduction of water (5 per cent of their body weight) into their stomachs and, in addition, the injection of 2.5 c.c. of water subcutaneously along the dorsal spine. Urine was collected and measured at 30 minute intervals for a 3 hour period. Following an hour of rest, the same animals were rehydrated and 2.5 c.c. of test plasma was injected subcutaneously along the dorsal spine. The output was again measured for a 3 hour period. The urinary outputs were plotted against time on arithmetic millimeter graph paper and the area beneath these volume-time curves was measured with a compensating polar planimeter. A comparison of the areas beneath the output curves provided a measure of the degree of antidiuretic activity in the plasma. This was expressed as a percentage, i.e., the area beneath the second curve was a certain per cent of the area beneath the first. The area measurement integrated volume and time and, as expected, proved to be considerably more sensitive and reliable than the measurement of volume alone.

In these studies, approximately 20 c.c. of whole blood was drawn from the antecubital vein of each patient and immediately heparinized with 2 drops of liquid heparin for each 5 c.c. of blood. The sample was centrifuged at 2,300 g for 30 minutes, and the plasma was removed and was used unaltered.

Material

The patients used in this study were carefully selected from the inpatient departments of the Division of Obstetrics and Gynecology of the City of Memphis Hospitals. Except in cases of toxemia, the patients used were normal in all respects, and were hospitalized for at least 12 hours prior to the taking of blood samples. Blood samples from toxemia patients were drawn immediately upon admission and when possible before therapy was instituted.

For the purposes of this work the following classifications of toxemia were applied: (1) cases were termed mild pre-eclampsia if the patient's blood pressure was greater than 140/90 and less than 160/100 and if they showed edema or albuminuria; (2) the requirements for severe pre-eclampsia were met if the patient's blood pressure was over 160/100 and if a 2 plus edema was present; (3) patients who experienced a convulsion in the presence of a member of the house staff or the referring physician regardless of the degree of blood pressure elevation, edema, or albuminuria were classified as having eclampsia.

The treated patients with eclampsia were studied 4 to 6 days after the induction of fluid and symptomatic therapy as outlined by Turner,[10] whether the patient had or had not been delivered. If hypertensive cardiovascular disease or renal disease were encountered, these patients were eliminated from the study.

Results

Plasma From Nonpregnant Patients.—Ten patients were given fluids amounting to 3 per cent of their body weight. One half of this volume was given intravenously and one half orally—the entire volume was given in one hour. Theoretically, this superhydration diluted the existing ADH and lowered the plasma crystalloid osmotic pressure which stimulated the osmoreceptors and reflexly arrested the secretion of ADH so that circulating antidiuretic substance was at a minimum.

Blood was drawn before and after hydration and ADH assays were made. The plasma drawn before hydration produced a curve the area of which was 55 per cent of the control curve; after hydration the output curve was 88 per cent of the control.

It should be noted that a 100 per cent urine return occurred following subcutaneous injection of water in the test animal but only 88 per cent return was found upon testing hydrated plasma. This difference probably represents other substances in the plasma because the ADH activity was forced to an irreducible minimum by the hydration procedure and theoretically the return should have equaled 100 per cent.

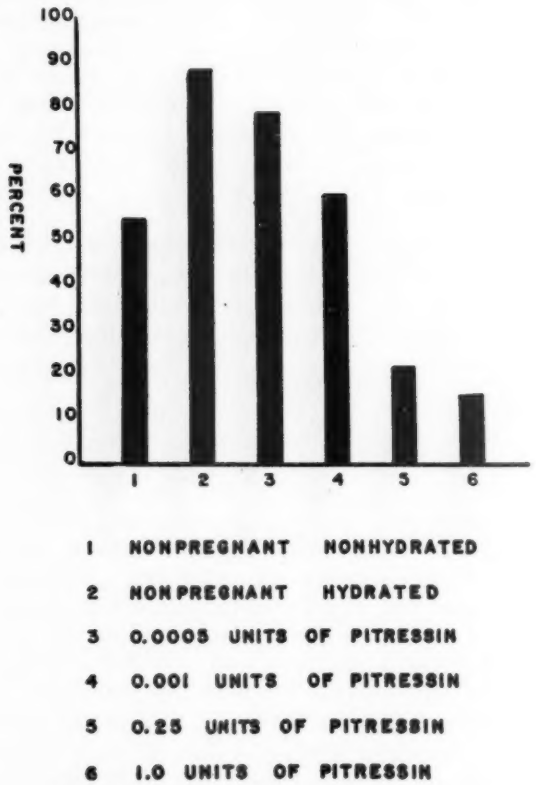

Fig. 1.—Time-urine output integration, expressed as per cent of control output, in response to the subcutaneous injection of the indicated plasma or Pitressin solution.

Serial Dilution of Pitressin With Plasma From Hydrated Patients.*—To establish a set of standards, serial dilutions of commercial Pitressin were made with the use of plasma from hydrated patients. It was found that, as the concentration of Pitressin was increased, the area under the volume-time excretion curves was decreased. Plasma from 40 nonpregnant superhydrated female patients was used to make the Pitressin dilutions.

0.0005 Unit of Pitressin: When 0.0005 of a unit of Pitressin per 100 grams of body weight of test animal was added to 2.5 c.c. of plasma from superhydrated patients, the average area under the resultant output curves was 79 per cent of the control. This minute amount of Pitressin was enough to elicit a 10 per cent difference from the superhydrated plasma alone.

*Pitressin was supplied by Parke, Davis & Company, Detroit, Mich.

0.001 Unit of Pitressin: One-thousandth of a unit of Pitressin per 100 grams of body weight of test animal was added to 2.5 c.c. of plasma from superhydrated patients. The resulting volume-time curve had an average area of 61 per cent of the control curve. This is 32 per cent less than the area inscribed by superhydrated plasma alone.

0.25 Unit of Pitressin: The addition of 0.25 unit of Pitressin per 100 grams of body weight of test animal to 2.5 c.c. of plasma from superhydrated patients produced a volume-time curve with an area of 22 per cent of the control. This curve is 75 per cent less than that of superhydrated plasma alone.

1.0 Unit of Pitressin: When 1 unit of Pitressin was added, the resultant area was 16 per cent of the control value. This gave a difference 82 per cent less than that of superhydrated plasma alone. More Pitressin did not produce a greater effect. Thus, the maximum antidiuretic activity found was between 15 and 20 per cent of the control and this was produced by one unit of Pitressin per 100 grams of body weight of test animal.

The composite results of all of these experiments are presented in a bar graph (Fig. 1).

Normal Term Pregnancy.—In this study of toxemia, the normal term pregnant patient was used as the control. The plasma antidiuretic activity of 10 term pregnant patients with no signs of toxemia or history of renal or cardiovascular disease gave a response which was 82 per cent of the control.

Mild Pre-eclampsia.—Nine patient with mild pre-eclampsia were studied. These patients were those who exhibited a rapid weight gain or increase in blood pressure and were admitted to the hospital.

The antidiuretic test effect of the 9 patients studied averaged 76 per cent of the control.

Severe Pre-eclampsia.—Seventeen patients with severe pre-eclampsia gave a return which was 49 per cent of the control. Thus, these patients exhibited a marked antidiuretic activity.

Eclampsia.—Twelve third-trimester pregnant patients with eclampsia were included in this series. Contrary to expectation, the trend was reversed and a 57 per cent return, when compared to the control, was revealed.

Eclampsia After Treatment.—Six of these patients with eclampsia were studied following the hydration treatment outlined by Turner.[10] After 4 to 6 days of treatment, regardless of the condition of the patient, response, or termination of pregnancy, the response was 81 per cent of the control.

Comment

Before entering the study of antidiuretic activity in the plasma of toxemic patients, it was decided that the normal ADH concentration in nonpregnant female patients should be estimated. Blood was drawn before and after hydration of these patients and ADH assays were made. The plasma drawn before hydration produced a curve the area of which was 55 per cent of the control curve, but the plasma from these patients after hydration produced an average area which was found to be 88 per cent of the control and was thought to represent the irreducible minimum of ADH activity in human subjects as revealed by this method.

To establish a standard curve from known amounts of Pitressin, dilutions were made with the plasma from the hydrated nonpregnant female as the diluent.

The normal term pregnant patient exhibits very little antidiuretic activity as shown by an 82 per cent return. Since plasma from the normal nonpregnant female allows but a 55 per cent return, this leads to the belief that the term pregnant patient is either well hydrated, has a decreased production of ADH, or has an increased destruction or excretion of this hormone. The latter view could well add to the usual explanation of increased diuresis in the last 2 or 3 weeks of gestation.

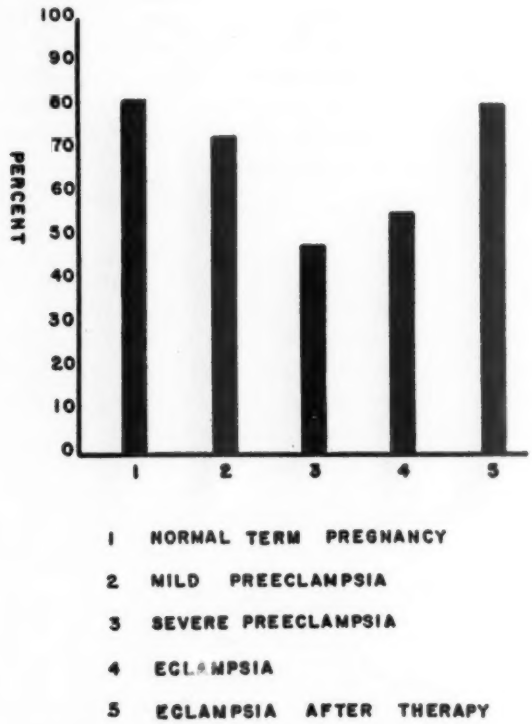

Fig. 2.—Time-urine output integration, expressed as per cent of control output, in response to the subcutaneous injection of the indicated plasma.

Although the number of patients studied with mild pre-eclampsia was small (9), it is felt that the results are worthy of comment. The antidiuretic activity response was 76 per cent, or 8 per cent greater than the response from the normal term pregnant patients. The difference is not remarkable, but one would not expect too much of a shift away from the normal in the mildly toxemic patient. Compared with the serial dilutions, 2.5 c.c. of the plasma of the patient with mild pre-eclampsia contained approximately 0.0005 unit of antidiuretic activity per 100 grams of rat (Fig. 2).

The morbidity of the patient with severe pre-eclampsia is often underestimated. Experience indicates that severe pre-eclampsia is frequently more grave, more critical, and more difficult to manage than eclampsia. The ADH activity response was 49 per cent of the control, showing the highest level encountered. By comparison, the plasma of the average patient with severe

pre-eclampsia exhibits more antidiuretic activity than that of the normal non-pregnant woman, and is favorably related to the ADH activity of 0.001 unit of Pitressin per 100 grams of rat.

In the 12 patients with eclampsia studied, the blood pressure varied from 130/90 to 210/160 and the edema from none to 4 plus. Regardless of blood pressure elevation, amount of edema, or degree of albuminuria, the 12 patients comprising the eclampsia group had at least one convulsion in the presence of a member of the house staff. Furthermore, although the patients with mild and severe pre-eclampsia were studied prior to sedation, the eclamptic patients were given an intravenous sedative (sodium Amytal, 7½ grains) and sent to the eclampsia ward where blood was drawn for assay.

In this somewhat physiologically heterogeneous group, it is perhaps not surprising that the average plasma antidiuretic activity was measurably less than in the more functionally uniform severe pre-eclampsia series. In addition to the heterogeneity of physical findings, it is possible that the intravenous induction of sedation may have produced sufficient depression of the hypothalamus to have inhibited ADH production.

Six of the eclamptic patients were selected at random and a second measurement of their plasma ADH level was made 4 to 6 days following hydration therapy as outlined by Turner.[10] In this group, the animal response was 81 per cent of control—a figure which is indistinguishable from that of the normal term pregnant patient. Such a finding lends considerable significance to hydration therapy and further indicates that pathologic elevations of plasma ADH occur in the toxemias of pregnancy and are amenable to therapy.

Summary and Conclusions

1. The degree of antidiuretic activity in the plasma of 54 patients with toxemia of pregnancy was assayed against a standard curve based on serial dilutions of commercial Pitressin.

2. Evidence is presented that a definite increase in plasma antidiuretic activity occurs in toxemia of pregnancy which is related to the clinical severity of the disease.

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A CARBONIC ANHYDRASE INHIBITOR AS A DIURETIC IN OBSTETRICS*

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OUR inadequate knowledge concerning the etiology of toxemia of pregnancy has led us to treat this clinical entity empirically. Eclamptic convulsions are managed by sedation or parenteral magnesium sulfate. Hypertension is treated by sedation and hypotensive drugs. Fluid retention is controlled by the restriction of sodium and water as well as by the use of diuretics. The definitive treatment of toxemia of pregnancy, however, is delivery of the infant.

This study was made in an effort to determine the usefulness of the diuretic, Diamox, 2-acetylamino 1,3,4-thiadiazole-5-sulfonamide (acetazoleamide), a carbonic anhydrase inhibitor, in controlling fluid retention in pregnancy.

Pharmacological Action of Diamox

Diamox is a potent carbonic anhydrase inhibitor which as such decreases the production of hydrogen ions in the renal tubular cells.[1]

$$H_2O + CO_2 \xleftrightarrow[\text{Anhydrase}]{\text{Carbonic}} H_2CO_3$$

$$H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

As a consequence of the diminished availability of hydrogen ions in the renal tubules, there is an excretion of bicarbonate, sodium, and potassium ions with an accompanying water diuresis. The loss of bicarbonate causes a metabolic and respiratory acidosis, which in turn causes a stimulation of renal acidification that prevents a further loss of sodium, potassium, and bicarbonate.[2] This balance is delicate, thus the serum levels of sodium and potassium remain within normal limits. If excessive sodium, potassium, bicarbonate, or water is not present, Diamox will not cause a significant diuresis of these substances.[3] In the presence of normal renal function and an excess of sodium and potassium, however, Diamox will effect a diuresis until the expanded extracellular volume approaches normal. Further medication will be ineffective until there is a reaccumulation of additional bicarbonate, cations, and water.

*Supported in part by a grant from United Cerebral Palsy.

The optimum dose of Diamox is 250 to 500 mg. each day. Higher dosage does not increase the diuretic action, but causes an increased incidence of such side effects as headache, dizziness, numbness, tingling of the extremities and face, and drowsiness.[4] The drug becomes effective in 45 minutes to one hour and continues its action for 6 to 8 hours. There follows a recovery period with retention of sodium and potassium. This cycle of loss of cations causing retention of bicarbonate necessitates an intermittent dosage schedule such as 250 to 500 mg. of Diamox each day for 3 to 4 days, then discontinued for 3 to 4 days.[5] Parenteral use of acetazoleamide is not necessary unless there is nausea or vomiting, since oral administration of the drug is effective.

Method of Study

Diamox has been used therapeutically in 65 private patients and 20 hospitalized clinic patients. In 28 patients there was sufficient time and patient cooperation to permit 24 hour collections of urine for electrolyte determinations. The most illustrative data of these electrolyte excretions are presented for 15 of these patients.

A diuretic index was used to evaluate the effect of Diamox (Table I). This index was modified after Kattus[6] and is based upon weight loss and urine volume, as well as sodium and potassium excretion. A 3 day control period preceded the 3 day therapy with Diamox unless induction of labor was mandatory.

TABLE I. INDEX OF DIURETIC RESPONSE

WEIGHT LOSS (POUNDS)	INCREASE IN URINE VOLUME (C.C./24 HOURS)	INCREASE IN NA EXCRETION mEq./24 HOURS	INCREASE IN K EXCRETION mEq./24 HOURS	POINTS TOWARD INDEX
Less than 1	Less than 200	Less than 25	Less than 25	0
1-2	200- 500	25-50	25-50	1
2-3	500-1,000	50-100	50-100	2
3-4	1,000-2,000	100-150	100-150	3
4 and above	2,000 and above	150 and above	150 and above	4

Except for the control patients in Table II, Diamox was not used unless there was evidence of fluid retention.

At the initial prenatal examination, patients were placed on a 2,000 to 2,500 calorie high-protein and high-vitamin diet which contained about 2 Gm. of sodium. It was recommended that no salt be added at the table and foods high in sodium were to be eliminated from the diet. Despite the emphasis placed on the restriction of sodium, many patients did not adhere closely to the suggested diet.

When there was evidence of fluid retention, private patients were asked to make 24 hour collections of urine during control periods and during Diamox therapy. Urine collections were made on clinic patients only during hospitalization since it was felt that samples from these ambulatory patients would not be complete. Twenty-four hour collections of the control samples therefore represented the sodium intake at the time Diamox was required. Further reduction in the patient's sodium intake was not made until after Diamox therapy. The exceptions to this were the control patients in Table III, patient D. P. in Table IV, and the hospitalized clinic patients in Table VI. All of the patients in Table VI were on a 300 to 500 mg. sodium diet during the control and Diamox therapy.

TABLE II. CONTROL OBSTETRICAL PATIENTS TREATED WITH DIAMOX (NO EDEMA OR HYPERTENSION)

PATIENT	AGE	PARITY	GESTATION	INFANT	DOSE (MG./DAY)	DURATION COURSE (DAYS)	WEIGHT CHANGE		URINE VOLUME		Na EXCRETION		K EXCRETION		DIURETIC RESPONSE
							CONTROL PERIOD	DRUG PERIOD	CONTROL PERIOD (C.C./24 HOURS)	DRUG PERIOD (C.C./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	
M. B.	30	ii-0-0-ii	38 weeks, normal	Normal	250 mg.	3	0	−1½	1,442	2,055	132	113	91	115	0.75
E. H.	25	0	36 weeks, normal	Normal	250 mg.	3	0	−1¼	1,368	1,998	112	107	62	100	1.00
S. P.	24	0	38 weeks, normal	Normal	250 mg.	3	+¾	−1	1,480	1,570	98	109	89	92	0.25

Effect of Diamox

Patients With No Edema or Hypertension.—It was desirable to determine the effect of Diamox on normal pregnant patients who had no manifestations of toxemia or fluid retention. Table II contains the data on 3 normal primiparas near term who received Diamox for 3 days. It is evident that all of these patients lost 1 to 1½ pounds in 3 days but failed to excrete impressive amounts of sodium or potassium. Two of these patients noted increased thirst and at the conclusion of the drug period regained the lost weight in one day.

It is evident that Diamox does not cause a significant elimination of sodium or potassium in patients who have not had an abnormal retention of these cations. Diamox, however, has no adverse effect upon normal pregnant patients and a therapeutic trial of the drug is not contraindicated when there is a question of excessive sodium, potassium, and fluid retention.

Patients With Edema but Without Hypertension.—One hundred private patients have been seen with evidence of fluid retention but without hypertension. Fluid retention is defined as 2 plus edema and a weight gain of 2 pounds in one week. When this condition was noted, the causes of weight gain and sodium and water retention in obstetrics were discussed. Diets were reviewed and foods high in salt were eliminated. In 35 of these patients, a discussion of sodium intake and modification of their diet, and in some instances bed rest and elevation of the extremities, resulted in the correction of the fluid retention.

In 65 cases, a discussion of fluid retention and a review of the diet was not successful in eliminating edema. Diamox was then used as a diuretic. One course was sufficient in 22 patients, 2 courses in 29, and 3 or more courses were necessary in 14 patients.

The weight losses in these two groups of private patients are compared in Table III. It is evident that the weight loss in patients on a 700 mg. to 1 Gm. sodium diet was smaller and less rapid than in the patients given Diamox. The patients who adhered to a low-sodium diet were cooperative women, however, and diuretics were not necessary during their pregnancies. Unless patients given Diamox reduced their sodium intake, a "rebound phenomenon" occurred, with the retention of sodium and water essentially nullifying the effects of the drug. Therefore, patients with impending toxemia of pregnancy were placed on a 700 mg. to 1 Gm. sodium diet. This was recommended for the remainder of the pregnancy.

TABLE III. COMPARISON OF WEIGHT LOSS IN PATIENTS TREATED WITH A LOW-SODIUM DIET WITH THAT OF PATIENTS TREATED WITH DIAMOX

	POUNDS LOST			
	0-1	1-3	3-5	5-8
Low-sodium diet 5 days (No. of patients)	6	18	8	3
Diamox 3 days (No. of patients)	6	23	26	10

Illustrative data on the electrolyte excretion of these ambulatory patients is presented in Tables IV and V. It is noted that there was a diuresis of sodium, potassium, and water in all of these patients. The diuretic index was consistent with the amount of sodium, potassium, and water which was retained. The largest excretion of sodium was 286 mEq. in 24 hours. The

TABLE IV. PATIENTS TREATED WITH DIAMOX WHO HAD EDEMA BUT NO HYPERTENSION

PATIENT	AGE	PARITY	GESTATION	EDEMA	INFANT	DOSE (MG./DAY)	DURATION COURSE	WEIGHT CHANGE		URINE VOLUME		NA EXCRETION		K EXCRETION		DIURETIC RESPONSE
								CONTROL PERIOD	DRUG PERIOD	CONTROL PERIOD (C.C./24 HOURS)	DRUG PERIOD (C.C./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	
S. H.	22	0	37 weeks	2+	Normal	750	3	0	−5	1,825	3,340	147	236	62	118	2.75
D. P.	20	0	37 weeks	2+	Normal	750	3	0	−1½	1,430	2,452	27	81	47	64	1.5
M. J.	23	0	38 weeks	2+	Normal	500	2	0	−3	1,315	2,860	110	162	99	128	2.25
J. J.	18	0	24 weeks	2+	Normal	750	1	0	−1¼	1,288	2,120	136	150	46	114	1.25
J. C.	25	0	36 weeks	2+	Normal	250 I. V.	3	−1½	−3½	1,385	2,250	108	140	89	117	1.5

TABLE V. EFFECT OF DIAMOX AND A LOW-SODIUM DIET ON AN OBSTETRICAL PATIENT WITH EDEMA BUT NO HYPERTENSION

M. R. 25-YEAR-OLD WHITE PARA 0 NORMAL INFANT 2 TO 3 + EDEMA	TREATMENT	WEIGHT CHANGE		URINE VOLUME		Na EXCRETION		K EXCRETION		DIURETIC RESPONSE
		CONTROL PERIOD	DRUG PERIOD	CONTROL PERIOD (C.C./24 HOURS)	DRUG PERIOD (C.C./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	
First series	500 mg. daily 3 days	+1	−4	2,045	3,325	135	236	67	107	2.75
Second series, one week later	500 mg. daily 3 days	0	−3	1,968	3,058	176	191	67	104	1.75
Third series, after 500-700 mg. sodium diet for 10 days	500 mg. daily 2 days	0	−2	1,704	2,595	94	95	58	87	1.25
Fourth series, after 500-700 mg. sodium diet for 20 days	500 mg. 2 days	0	0	1,765	2,100	62	70	49	53	0.25

TABLE VI. PATIENTS TREATED WITH DIAMOX WHO HAD EDEMA AND HYPERTENSION

PATIENT	AGE	PARITY	GESTATION	DISEASE AND SYMPTOMS	DOSAGE	DURATION TREATMENT	WEIGHT CHANGE		URINE VOLUME		Na EXCRETION		K EXCRETION		AVERAGE BLOOD PRESSURE		DIURETIC RESPONSE
							CONTROL PERIOD	DRUG PERIOD	CONTROL PERIOD (C.C./24 HOURS)	DRUG PERIOD (C.C./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	CONTROL PERIOD (mEq./24 HOURS)	DRUG PERIOD (mEq./24 HOURS)	CONTROL	3 DAYS AFTER TREATMENT	
R. J.	31	0	28 weeks	Acute toxemia Chronic hypertensive disease Diabetes mellitus	250 mg. each day	3 days	–2	–11	894	3,573	107	396	13	16	185/105	165/95	3.0
L. H.	19	0	34 weeks	Acute toxemia Edema 1+, albuminuria 1+	500 mg. each day	2 days	–4	–4	3,878	3,567	165	255	58	32	130/90	130/90	0.50
A. B.	30	iii-0-0-ii	37 weeks	Chronic hypertension with toxemia Albuminuria 2+, edema 2+	500 mg. each day	3 days	–½	–3	1,400	2,120	29	63	42	97	170/94	178/96	1.75
N. C.	34	v-i-ii-iii	38 weeks	Chronic hypertension with toxemia Albuminuria 1+, edema 2+	750 mg. intravenously	1 day	–5	–5	2,225	2,683	126	166	34	65	150/100	138/90	0.75
L. F.	31	ii-0-0-ii	36 weeks	Eclampsia Albuminuria 3+, edema 2+	750 mg. intravenously	1 day	–1	–1½	2,235	3,180	12	77	12	26	190/120	200/120	1.0
L. H.	18	0	36 weeks	Acute toxemia Albuminuria 3+, edema 2+	500 mg. each day	1 day	—	—	1,875	1,950	5.5	3.9	15.5	19.5	155/115	150/115	0

excretion of sodium usually followed a typical pattern. If the excretion of this electrolyte was 110 mEq. per 24 hours during the control period, approximately 250 mEq. of sodium would be lost during the first 24 hours, 196 meq. the second day, and 116 mEq. the third. It was evident, therefore, that the optimum use of Diamox consisted of a 3 day course.

The need for, as well as the effectiveness of, a low-sodium diet in conjunction with Diamox therapy is shown in Table V. This ambulatory patient collected her urine for laboratory analysis for 60 days. With the initial development of fluid retention a 3 day course of Diamox was given. There was an excellent diuresis with a diuretic index of 2.75. Despite dietary counseling, there continued to be an excessive weight gain and fluid retention. A second course of Diamox was given one week later. This resulted in a satisfactory diuresis of sodium, potassium, and water, resulting in a diuretic index of 1.75. The patient was placed then on a 500 to 700 mg. sodium diet. Ten days later a third course of Diamox was given. There was a marked reduction in the urinary excretion of sodium indicating adherence to the diet. The diuretic index for this Diamox course was 1.25. After 20 days on the low-sodium diet, Diamox was unnecessary and ineffective.

Patient D. P. in Table IV presented a similar situation although urine was not collected until the second course of Diamox. Her excretion of electrolytes showed that she was adhering to a low-sodium diet. She had no further problem with fluid retention during her pregnancy.

Patients With Edema and Hypertension.—Diamox was given to 20 hospitalized patients with toxemia of pregnancy. Six typical responses to the drug are presented in Table VI. All patients were on a 300 to 500 mg. sodium diet and were at bed rest.

Patient R. J. showed the most favorable response to Diamox. This primipara had diabetes mellitus and chronic hypertensive disease with superimposed acute toxemia. The average daily blood pressure was 185/110; there was 3 plus edema but no albuminuria. Three days of Diamox therapy resulted in a 9 pound weight loss and the excretion of 1,188 mEq. of sodium; 796 mEq. of these were excreted in one 24 hour period. There was a diuretic index of 3. Serum sodium and potassium remained normal. Following the cessation of Diamox therapy, the patient continued to excrete increased quantities of electrolytes and water on bed rest and a low-sodium diet. There was a total weight loss of 37 pounds in 2 weeks.

Patients L. H. and N. C. were similar to R. J. in their ability to excrete sodium and water on bed rest and a low-sodium diet. In both patients the same amount of weight was lost during the control period as during the drug period; the excretion of sodium was enhanced by Diamox, however. Because of the weight loss during the control period the diuretic index was only 0.50 and 0.75.

A carbonic anhydrase inhibitor was helpful in these 3 patients, but the same results would probably have occurred less rapidly without specific medication.

Patients A. B., L. F., and L. H. are typical examples of severly ill toxemic patients. The process was irreversible without delivery. These women were not oliguric, but they had failed to effect a satisfactory sodium and water diuresis on a low-sodium diet and bed rest. Diamox caused a twofold increase in sodium excretion in patient A. B. and a sixfold increase in patient L. F. This loss of sodium, however, was unimportant in the management of these patients. There was no clinical improvement until delivery.

Comment

One cannot conclude from these data that Diamox and a low-sodium diet will prevent patients from developing toxemia of pregnancy, but the incidence of toxemia in cooperative and intelligent patients who maintain good nutrition and a low-sodium diet is extremely low.

In patients with fulminating toxemia or eclampsia, a diuretic can be used only hopefully and empirically. It cannot be expected to effect a diuresis of sodium and water in the presence of a reduced rate of filtration at the glomerulus.[7] Moreover, a diuretic cannot be expected to overcome the profound alteration in extracellular electrolyte and water imbalance that is present in severe toxemia.[8] Diamox can, however, serve as an adjunct in the treatment of those toxemic patients who can effect some degree of diuresis on bed rest and a low sodium diet. No ill effects were noted when the drug was administered to severely ill patients. In patients with severe renal impairment, however, Diamox as well as a low-sodium diet must be used with caution.

Although the fetus has an extremely low level of carbonic anhydrase, no fetal deaths could be attributed to Diamox therapy.

Conclusions

1. Diamox is a potent diuretic when administered to patients who have sodium and water retention and normal renal function. The drug should be used with a low-sodium diet to control fluid retention in pregnancy.

2. Patients who received Diamox had no greater hypotensive response than those who were treated without specific therapy.

3. Diamox is essentially ineffective in patients who have severe toxemia of pregnancy, eclampsia, a reduction in glomerular filtration, impaired renal function, or a profound electrolyte imbalance.

Appreciation is expressed to Dr. Louis G. Welt, Department of Medicine, University of North Carolina, for the use of his flame photometer and his assistance in this study. Appreciation is also expressed to Miss Genevieve Lowry and Mrs. Martha Simpson for their technical assistance.

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CEREBRAL HEMORRHAGE IN A PATIENT WITH ECLAMPSIA

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SEVERE cerebral hemorrhage is not rare in eclampsia. Dieckmann[4] and Hammond[6] noted that a compilation of reports indicated that extensive cerebral hemorrhage is found in 15 to 20 per cent of the autopsies in eclampsia.

The following case of a fatal cerebral hemorrhage in a postpartum eclamptic patient is reported because the insidious onset of the disease and lack of prominent clinical symptoms created diagnostic difficulties.

Report of a Case

L. G. (A-1957), a 29-year-old white woman, para ii, gravida iii, was admitted for the third time to St. Mary's Hospital on July 27, 1956, at term and in labor. The blood pressure on her first admission to this hospital in September, 1954, for her first full-term normal spontaneous delivery was 120/60. She was admitted the second time on March 20, 1956, in false labor, at which time the blood pressure was 90/50. Examination on July 27, 1956, the day of the third and last admission, showed edema and a blood pressure of 130/90. The heart and lungs were not remarkable.

Laboratory examination showed a hematocrit of 38 per cent, and a white blood count of 20,000 with 90 per cent polymorphonuclear leukocytes. The specific gravity of the urine was 1.030 and albumin and sugar were not found.

The fetus, presenting as a right occiput posterior, was rotated with forceps with no undue difficulty. The first stage of labor lasted 11 hours, the second stage 47 minutes, and the third stage, 3 minutes. On July 27, 4 hours after delivery of a normal baby and the entire placenta, without warning or complaints, the patient had a convulsion with labored and irregular breathing. The left pupil was dilated. The blood pressure rose to 150/110, and the temperature to 104.6° F. A lumbar puncture the following morning disclosed increased pressure and bloody spinal fluid. On July 28, 1956, 12 hours after the onset of convulsions, the patient developed anuria which changed to oliguria. The blood nonprotein nitrogen was 48 mg. per cent and uric acid was 6.7 mg. per cent. Coma and intermittent convulsions continued until her death 50 hours after the onset and 54 hours after delivery. The final clinical diagnosis was subarachnoid hemorrhage, etiology unknown.

Autopsy Findings.—

Gross: The kidneys were normal in size and weight and hemorrhages were not seen on section. The brain weighed 1,700 grams and showed flattening of the sulci and gyri of the left hemisphere. Section showed a massive hemorrhage in the left hemisphere, lacerating the brain substance (Fig. 1), and a smaller hemorrhage in the left occipital lobe (Fig. 2). The lower lobes of both lungs contained many focal gray consolidated areas.

Microscopic: Most of the glomeruli of the kidneys were ischemic and slightly enlarged (Fig. 3). The vessels and tubules were not remarkable. The vessels of the brain showed acute arteriolonecrosis with hyaline degeneration and fibrinoid smudging of the walls (Fig.

4). Brain tissue adjacent to the damaged vessels contained extravasated red blood cells. There was extensive fresh hemorrhage in the pia-arachnoid. Extensive acute pneumonitis was disclosed in sections of the lower lobes of both lungs.

Pathological Diagnosis.—Eclampsia with arteriolonecrosis of cerebral vessels, extensive left cerebral and occipital hemorrhages, bilateral aspiration lower lobar pneumonia.

Fig. 1.—Massive left intracerebral hemorrhage.

Fig. 2.—Hemorrhage in left occipital lobe.

Comment

The diagnosis of postpartum convulsions due to eclampsia was considered but not made in this case, because of the lack of prominent clinical symptoms. The blood pressure of 130/90 on admission was not considered elevated.

In retrospect, however, it was significantly higher than the 90/50 reading taken 4 months earlier. Edema, although present, was not prominent. Perhaps undue importance was placed on the absence of albuminuria in one urinalysis. Unfortunately, this test was not repeated. Soon after the onset of convulsions the blood pressure rose to 150/110, and oliguria with a moderate elevation of blood nonprotein nitrogen was noted.

Fig. 3.

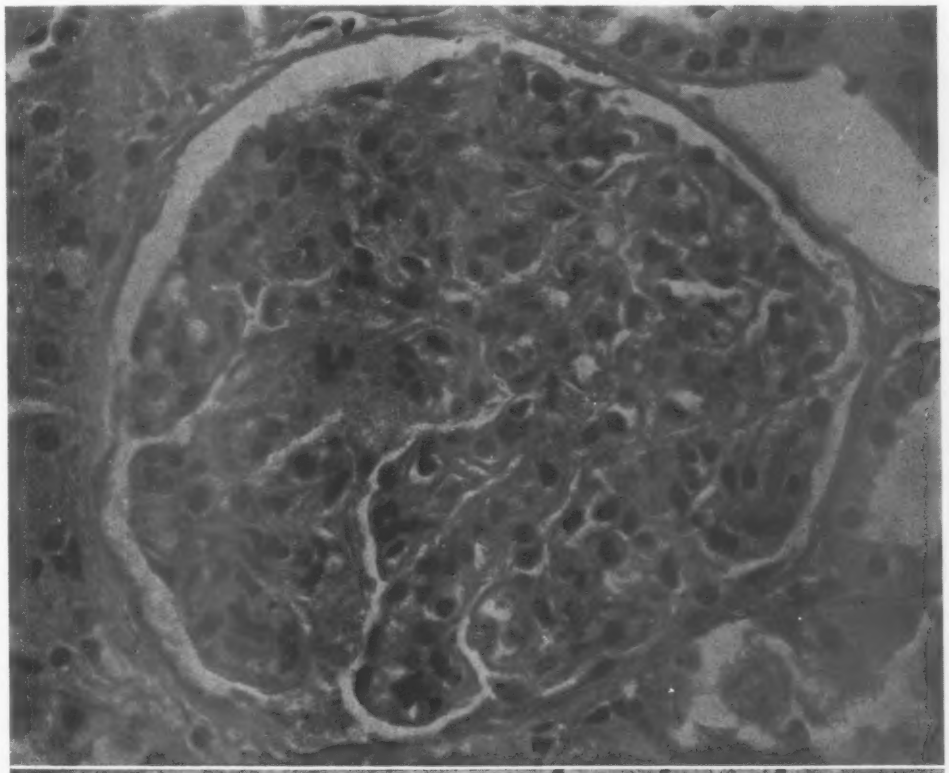

Fig. 4.

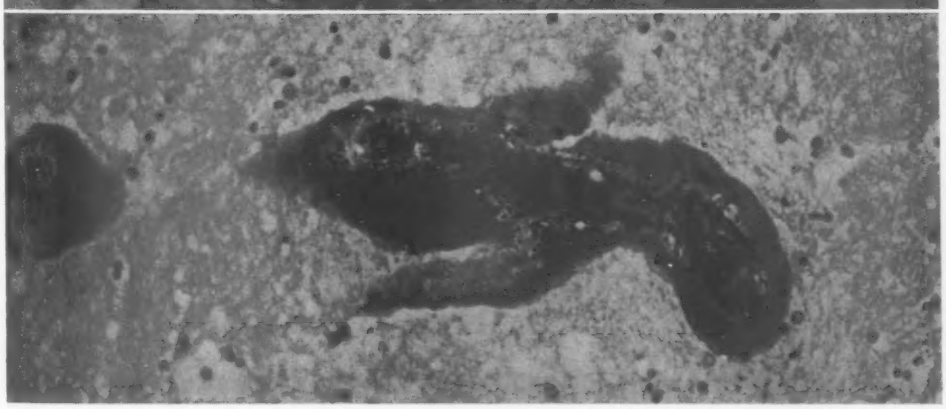

Fig. 3.—Ischemic glomerulus. (Hematoxylin and eosin. ×590; reduced ⅙.)
Fig. 4.—Small cerebral vessels with irregularly thickened smudged necrotic walls. (Hematoxylin and eosin. ×300; reduced ⅙.)

Brougher[2] reported a similar case of fatal postpartum cerebral hemorrhage in which there were few antecedent warnings of toxemia. Autopsy disclosed

arteriolar spasm in the brain and kidneys in addition to massive intracerebral hemorrhage.

The specificity of the pathological lesions of eclampsia is far from settled. Bell[1] and Canny[3] asserted that renal lesions are specific for eclampsia. The glomerulus is swollen and the capillary wall swollen and widened, resulting in a bloodless glomerulus. Sheehan[7] described thickening of the endothelium of the afferent arteriole of the glomerular tuft. The resulting narrowing of the lumen of the arteriole may result in intermittent periods of ischemia of the glomerulus. Dieckmann and associates[5] described the results of study of renal biopsies taken from 71 pregnant patients with toxemia. Thickening of the basement membrane and narrowing of glomerular capillaries were found in the patients with toxemia, as well as in 3 patients with glomerulonephritis and in 13 with hypertensive disease and in 4 with normal pregnancies. Dieckmann and his co-workers[4, 5] stated that there are no pathognomonic lesions of eclampsia. The renal lesion is not specific for eclampsia but is similar to that found in hypertensive disease and even in glomerulonephritis. The abnormality rests primarily in thickening of the afferent arteriole or wall of the glomerular capillary, so that ischemia of the glomerulus can result.

In this case, although no thickening of the afferent arteriole or glomerular capillaries could be demonstrated, glomerular ischemia was prominent in both kidneys (Fig. 3). The stimulus for the glomerular ischemia is postulated to be a toxin associated with pregnancy.[4] In this patient, the bilateral renal ischemia from many ischemic glomeruli (Fig. 3) may have been the basis for the hypertension which was followed by cerebral arteriolonecrosis and cerebral hemorrhages (Figs. 1, 2, and 4).

Conclusions

1. A fatal case of eclampsia with cerebral hemorrhages is presented.

2. Arteriolonecrosis of the cerebral vessels with unremarkable renal vessels and ischemic glomeruli were found.

The photomicrographs are by Antol Herskowitz.

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THE EFFECT OF TRIIODOTHYRONINE ADMINISTRATION ON THE ELEVATED PROTEIN-BOUND IODINE LEVEL IN HUMAN PREGNANCY*

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THE occurrence in human pregnancy of a physiological increase in the level of protein-bound or serum precipitable iodine (PBI, SPI) was first documented by Heinemann and associates.[1] The increase persisted after butyl alcohol extraction[3] and so represents the thyroxine fraction of the circulating iodinated amino acids.

Most of the explanations advanced to account for the rise in PBI have been recently summarized,[4] the most likely being an increase in binding capacity of the specific carrier proteins of the serum for thyroid hormone.[5, 6] In addition to these, however, there are three other mechanisms which could account for the elevated PBI: (1) a change in the setting of the pituitary-thyroid "servo" mechanism[7]; (2) derangement of the normal pituitary-thyroid relation similar to that found in hyperthyroidism[8-10]; or (3) secretion of thyrotropin by the placenta, suggested by chemical extraction studies[11] and also, analogously, by the finding by Smith[12] of an adrenal weight-maintaining factor in the hypophysectomized pregnant monkey, presumably adrenocorticotrophin. The present experiments were designed to test these latter three possibilities.

Methods

Patients in the second and third trimesters of pregnancy were chosen at random from the Ante Partum Clinic of the Sloane Hospital. They had been appraised clinically and were considered to be undergoing uneventful pregnancy. After blood was drawn for determination of the PBI level, each patient received triiodothyronine, 75 to 125 μg, given once daily, by mouth, for 7 days. Blood for PBI was again drawn the morning after the last dose. PBI determinations were made in duplicate by the original method of Barker.[13]

Permission was obtained from the local radioisotopes committee to determine the 24 hour uptake of I^{131} in 2 patients ending their third month of pregnancy. Test doses of 15 μc I^{131} were given before triiodothyronine was administered and again on the eighth day of administration of the drug, according to the method described elsewhere.[9]

Results

The changes in the PBI level which followed triiodothyronine administration are shown in Table I; also, in 2 patients, the change in the 24 hour uptake

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of I^{131}. Decreases in the PBI level in excess of 1 μg per cent were induced at all months of pregnancy tested. This extent of change is beyond the error of the chemical method which has been estimated to be 0.5 μg per cent. Larger doses are seen to be required in the last 3 months of pregnancy, however. Some patients at each month of pregnancy failed to respond to the doses employed.

In the third to the sixth months of pregnancy, inclusive, the response to 75 μg of triiodothyronine is seen to be the same as that produced by 100 μg (Table I). This is in contrast to the last trimester in which the response to 75 μg differs significantly, at the 5 per cent level of significance, from that to 100 μg. The response to 75 μg in the earlier months is significantly different at the 1 per cent level from that induced in the later months by this dose.*

I^{131} uptake was decreased by treatment to the extent seen in nonpregnant healthy women.

TABLE I. EFFECT OF TRIIODOTHYRONINE ADMINISTRATION ON PBI LEVEL AND IN 2 PATIENTS ON 24 HOUR UPTAKE

MONTH	NO. OF PATIENTS	DOSE	AVERAGE PBI			PATIENTS WITH RESPONSE < 1 μG %		% I^{131} UPTAKE	
			INIT. μG %	FINAL μG %	DIFF. μG. %	NO.	%	INITIAL	FINAL
3	1	75	12.2	5.1	−7.1				
4	3	75	6.7	3.9	−2.7				
5	2	75	8.2	4.7	−3.5				
6	5	75	6.9	6.0	−0.9				
	11				Average −2.1	4	36		
3	1	100	6.2	2.6	−3.6				
4	0								
5	5	100	6.7	5.5	−1.2				
6	6	100	7.1	5.7	−1.4				
	12				Average −1.7	3	25		
7	3	75	8.1	7.2	−0.9				
8	5	75	6.2	5.4	−0.8				
9	8	75	6.8	6.3	−0.5				
	16				Average −0.75	9	56		
7	3	100	8.0	5.5	−2.5				
8	5	100	7.0	5.1	−1.9				
9	3	100	6.4	5.8	−0.6				
	11				Average −1.7	2	18		
9	4	125	6.7	4.9	−1.8				
3	1	75						18	7
3	1	75						15	8
	6								
Total	56								

Comment

The clear-cut decrease in both I^{131} uptake in early pregnancy, and PBI throughout the second and third trimesters of pregnancy, which followed the administration of triiodothyronine, parallels that of the normal individual given the hormone. It is not the failure of response seen in patients with toxic

*Assistance in the statistical analysis of the data was given by Dr. John W. Fertig of the Department of Biostatistics.

goiter.[14] Thus, there is no evidence that the abnormal pituitary-thyroid relation found in hyperthyroidism is present in pregnancy and hence such a change does not account for the increase in PBI.

Similarly, the present data tend to exclude the probability of formation and release of large amounts of thyrotropin by the placenta. It is unlikely that the placenta would be in a sensitive reciprocal relation with the thyroid such as has been found in the present study, in which an increase in available thyroid hormone resulted in a decrease in the level of PBI. In behalf of the concept of a placental secretion is the fact that, subsequent to the fifth month, the decrease in PBI which followed triiodothyronine administration was less than that which occurred before this time. Increased utilization of triiodothyronine in later pregnancy, however, would explain these results equally well (see below), without the necessity of invoking placental secretion as a mechanism.

In this regard, Akasu and co-workers[11] claim to have extracted a thyrotropic substance from placental tissue but their assay data are not convincing and, even if thyrotropin were extracted, the amounts they found were quite limited. Moreover, Smith[12] noted that thyroid weight, unlike adrenal weight, was not maintained after hypophysectomy in the pregnant monkey, and Greer[15] has made a similar observation in the rat.

The data, therefore, suggest that a normally responsive pituitary-thyroid relation is present in pregnancy, and that there is little if any thyrotropin secretion by the placenta. It is not established, however, whether the pituitary, and hence thyroid, is secreting at an increased rate. The fact that larger doses of triiodothyronine were required to lower the PBI level in later pregnancy suggests that the requirement for (i.e., production and turnover of) thyroid hormone may be increased. This would necessitate a sustained increase in the level of pituitary secretory activity.

Such a conclusion is also suggested by the increase in basal metabolic rate[16] and by the increase in I^{131} uptake[4] which occur normally during pregnancy. The extent of the rise in basal metabolic rate is limited, however, and such an increase could be accounted for by extrathyroidal mechanisms.[17, 18] Moreover, the disappearance rate of administered labeled thyroxine has been shown to parallel that of the nonpregnant woman,[19] although the technique is open to criticism because of errors resulting from recirculation of metabolized iodine. Thus it is still unsettled whether the turnover of thyroid hormone is or is not increased in pregnancy.

Other explanations could account for the finding that increasingly larger doses of triiodothyronine were required to depress the PBI as pregnancy advanced. The requirement of triiodothyronine to produce an effect could be on a per kilogram of body weight basis[20] so that more would be required as body and fetal weights increased during gestation. Also, triiodothyronine may be diffused into the amniotic fluid and hence enter a pool from which it becomes relatively unavailable to the tissues.

In view of the above uncertainties, the best explanation for the elevated PBI of pregnancy probably still remains the fact that there is an increase in binding capacity of the serum carrier proteins for thyroxine.[5, 6]

Summary

1. Depression of the elevated PBI level of pregnant women followed the administration of triiodothyronine in the second and third trimesters.

2. The data reveal that the pituitary-thyroid relation is normally responsive in pregnancy, and that the elevation in PBI is not due to the abnormal relation seen in hyperthyroidism.

3. The data tend to exclude the possibility of more than limited placental secretion of thyrotropin.

4. The implications are discussed of the finding that larger doses of triiodothyronine were required to suppress the PBI level in the last trimester of pregnancy than in the preceding trimester.

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PLASMA ALPHA-AMINO NITROGEN IN PREGNANCY*

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A NUMBER of recent investigators employing the Ninhydrin manometric method of Hamilton and Van Slyke have observed that the α-amino nitrogen concentration in plasma is decreased in pregnancy.[1, 3, 6] During the early puerperium amino nitrogen levels approximate those of the normal nonpregnant woman.[1, 3] The decrease observed does not appear to be related to changes in concentration of other blood constituents such as urea nitrogen or uric acid[1, 12] and varies independently of "combined" or peptide amino nitrogen, which is unaffected by pregnancy.[3] Of considerable interest in connection with this gestational hypo-amino-acidemia is the occurrence of higher amino acid levels in fetal than in maternal blood and, although recent evidence tends to support the thesis of active placental transfer, the actual basis for the inequality of amino acid nitrogen distribution across the placenta remains uncertain. Because of data indicating a role of hormone factors in the regulation of blood amino nitrogen levels,[9, 10] and in consideration of the known endocrine changes in gestation, the observations to be reported were made in an attempt to assess the importance of any influence of progesterone and estrogen on the plasma amino nitrogen in pregnancy and the early puerperium.

Material and Method

Normal puerperal women were selected for study. Those who developed morbidity or other complications were excluded from the series. Initially, one group of 10 patients received orally 60 mg. estrogen† daily beginning within 12 hours of delivery. A second group of 10 received this medication together with 100 mg. progesterone in oil intramuscularly. Treatment was maintained 5 days in all cases. Alternate untreated puerperas served as controls. Venous blood was obtained with minimal stasis on the fifth postpartum day after 18 hours' fasting. Heparin (Connaught) was used as an anticoagulant, 0.2 mg. per milliliter of whole blood. The cells were immediately separated by centrifugation, and protein-free picric acid filtrates of the plasma were prepared. The α-amino nitrogen concentrations of these filtrates were determined in duplicate by the method of Hamilton and Van Slyke.[11, 25] Blood urea nitrogen was determined on tungstic acid filtrates of plasma aliquots by a

*This investigation was supported in part by grants-in-aid from Parke, Davis & Company, Detroit, Mich., and Abbott Laboratories, North Chicago, Ill.

†Sulestrex (Abbott). Sixty milligrams is equivalent to 50 mg. sodium estrone sulfate.

steam distillation technique[3] and the amino nitrogen values corrected for urea hydrolysis. Total plasma protein concentration was estimated by the technique of Phillips and associates.[20] The values obtained were analyzed by the "t" test of Fisher.[23]

Further observations were made on an additional group of 20 patients who received 200 mg. oral estrogen* daily beginning within 12 hours of delivery. The α-amino nitrogen concentration of plasma was determined daily in the fasting state and the values compared with those of 10 normal control subjects who received no medication.

Observations

In Table I are shown the data for the lower dosage estrogen- and estrogen-progesterone-treated patients. Attention is directed to the close correspondence of the mean values for the two experimental groups which did not differ significantly from the controls. Blood urea nitrogen concentration was within the limits of normal for all subjects, the correction for urea hydrolysis amounting to approximately 0.10-0.15 mg. per cent as amino nitrogen. No significant differences between treated and control subjects were observed in the plasma specific gravity determinations, all values falling between 1.023 and 1.025, equivalent to 5.9 to 6.7 Gm. per cent protein, somewhat lower than expectancy for normal adults.[20]

TABLE I. PLASMA α-AMINO NITROGEN VALUES ON THE FIFTH POSTPARTUM DAY FOR ESTROGEN-TREATED (60 MG. SULESTREX), ESTROGEN- AND PROGESTERONE-TREATED (60 MG. SULESTREX, 100 MG. PROGESTERONE IN OIL) PATIENTS AND CONTROLS

ESTROGEN		ESTROGEN AND PROGESTERONE		CONTROLS	
PATIENT	COOH-N (MG. %)	PATIENT	COOH-N (MG. %)	PATIENT	COOH-N (MG. %)
B. E.	3.04	H. M.	4.23	A. J.	4.50
A. M.	4.12	K. N.	4.16	B. E.	4.37
J. A.	4.49	G. J.	4.12	C. S.	4.35
D. K.	5.02	L. M.	4.29	T. N.	4.30
D. N.	3.33	P. F.	4.27	N. E.	4.48
N. L.	4.02	C. E.	4.10	B. M.	4.61
S. P.	4.30	A. R.	4.21	L. I.	4.72
C. M.	4.22	I. L.	4.25	W. M.	4.53
C. N.	3.82	B. M.	3.82	E. G.	4.58
G. W.	3.83	B. R.	3.80	G. C.	3.67
Mean = 4.02 ± 0.59		Mean = 4.12 ± 0.18		Mean = 4.41 ± 0.17	

In Table II are shown the mean values and standard deviations for α-amino nitrogen determinations made on 20 puerperal subjects who received 200 mg. estrogen daily. The mean value of 3.39 ± 0.23 mg. per cent for this group corresponds closely with the control value of 3.41 mg. per cent (Table III). In general, within 48 hours of delivery the trend toward normal levels of amino nitrogen was well established. It is significant that comparable amino nitrogen values for estrogen-treated and control subjects were found, the postpartum increase in amino nitrogen concentration not being influenced by the hormone. Of incidental clinical interest was our failure to encounter "withdrawal bleeding" in any patient studied. Involution of the uterus was apparently not affected. The estrogen preparations, with or without progesterone, were well tolerated in all cases, no undesirable side effects being observed.

*Menagen (Parke, Davis). Two hundred milligrams is equivalent to 275 mg. sodium estrone sulfate.

TABLE II. MEAN PLASMA α-AMINO NITROGEN DATA FOR 20 PATIENTS WHO RECEIVED 200 MG. ESTROGEN (MENAGEN) FROM DAY OF DELIVERY TO FIFTH POSTPARTUM DAY. VALUES ARE NOT CORRECTED FOR BLOOD UREA NITROGEN

DAYS POST PARTUM	COOH-N (MG. %)	σ
0	3.39	±0.23
1	3.73	±0.32
2	4.07	±0.40
3	4.04	±0.36
4	3.89	±0.35
5	4.30	±0.14

TABLE III. PLASMA α-AMINO NITROGEN CONCENTRATION (MG. PER CENT) IN 10 POSTPARTUM PATIENTS WHO RECEIVED NO HORMONE. DATA NOT CORRECTED FOR BLOOD UREA NITROGEN

PATIENT	DAYS POST PARTUM					
	0	1	2	3	4	5
W. S.	3.84	3.80	3.74	4.26	4.06	3.83
H. R.	3.97	3.97	4.08	4.55	4.70	4.48
N. N.	–	3.56	3.80	4.13	4.71	4.70
L. T.	3.03	2.97	3.55	3.88	3.79	–
J. S.	–	3.30	3.37	3.98	4.26	4.55
G. N.	2.70	2.76	3.00	3.45	3.52	–
P. T.	–	3.70	3.96	4.46	4.27	4.38
D. S.	–	3.98	4.06	4.34	4.42	4.29
P. L.	–	3.24	3.40	3.71	3.80	3.89
E. S.	3.53	3.60	3.73	3.90	3.94	–
Means	3.41	3.49	3.67	4.07	4.15	4.30

Comment

The data presented fail to show any significant effect of estrogen or progesterone on the plasma amino nitrogen concentration of puerperal women. In both series of subjects studied, the postpartum rise in amino nitrogen proceeded unaffected by hormone treatment. In this connection it is of interest that the mean values for the patients who received 200 mg. estrogen were almost identical with those of the controls (Tables II, III). Although the regulation of amino acid concentration in blood has been shown experimentally to be subject to hormone control,[9, 10] our data suggest that other factors must be sought to account for the gestational decrease and postpartum reversion to normal levels of amino nitrogen.

It is conceivable that the hypervolemia and expansion of the extravascular space in pregnancy[4] could have a significant influence on the volume of distribution and concentration of certain blood constituents. The change in amino nitrogen concentration, however, does not parallel the observed trends in plasma volume and extravascular fluid. Moreover, the amino nitrogen levels appear to vary independently of peptide nitrogen, urea, or uric acid,[1, 3, 21, 24] observations inconsistent with simple dilution of amino acid by the body fluids of pregnancy.

Pertinent to the general problem of blood concentration of amino nitrogen are data showing increased urinary losses of amino acids. Increased histidine excretion in pregnancy is well established, the highest losses occurring between the third and eighth months.[17] Significant histidinuria is apparently not developed prior to the third month.[27] Evidently this paradoxical loss of amino acids in the face of positive nitrogen balances is based on altered renal dynamics with heightened excretion related to increased glomerular filtration as well as decreased tubular reabsorption.[18] Not only is histidine loss in the

urine increased, but tyrosine, serine, arginine, phenylalanine, threonine, and tryptophan are also excreted in significantly greater amounts.[26] It is possible that these losses might affect the blood level of amino nitrogen but direct data are not available relating to such an association which at present must remain speculative.

Bearing on the problem of hypo-amino-acidemia in pregnancy are the data showing differences in concentration of amino nitrogen across the placental barrier. Among the first observers of this differential concentration was Morse,[16] who found that fetal plasma was consistently higher in amino nitrogen than maternal plasma. The concentration gradient between the maternal and fetal circulation was attributed to active "absorption" by the placenta. Similarly Plass and Matthew[21] interpreted their data as indicating "selective absorption" of amino acids from maternal blood by the placenta, although Luck and Engle[14] attributed the unequal fetal-maternal amino acid distribution to Donnan equilibrium phenomena. Christensen and Streicher[5] concluded that the placenta is responsible for the unequal distribution of amino acids between the fetal and maternal circulations, the placenta actively transferring amino acids to the fetus, thereby causing lower maternal plasma levels. Such activity would appear to be a somewhat more complex physiological mechanism than simple diffusion of uric acid, urea nitrogen, creatine, and creatinine cross the placental barrier.[13, 21] Dent and his co-workers[8] also believed that active placental transfer of amino acids occurs and offered chromatographic data showing increased fetal concentration of individual amino acids studied. Other studies have quite consistently shown such fetal:maternal amino nitrogen differences in human pregnancy.[5, 7, 8, 12, 21] Comparable gradients have also been observed in the rabbit,[2, 5, 24] dog,[22] and guinea pig.[5] The concentration ratio of amino nitrogen between fetal and maternal plasma is between 1.6 and 1.8:1 for human pregnancy,[5, 7, 8] 5:1 for the guinea pig, and 1.5-2:1 for the rabbit.[5]

Direct evidence that trophoblastic tissue is capable of concentrating amino acids was given by McKay and associates,[15] who showed that fluid of hydatidiform moles contained twice the concentration of amino nitrogen of maternal serum, and Page[19] has observed that the D and L isomers of histidine behave differently with respect to placental transfer. The D isomer required 3 to 4 hours to reach equilibrium in the fetal circulation while L-histidine reached equilibrium in a matter of minutes, findings suggestive of an active transport mechanism for the passage of the natural isomer. The study of Clemetson and Churchman[7] is also pertinent to this problem. In toxemia of pregnancy or in cases of "cord obstruction" there occurred a decrease in the fetal:maternal amino nitrogen ratio. This change in ratio occurred by increase in maternal amino nitrogen levels which were found to exceed the normal expectancy for pregnancy and were believed to be the result of failure of placental transfer of amino acids.

In consideration of the foregoing studies the placenta may be considered as a "pump" or "kidney" which actively transfers certain maternal blood components to the fetus. The hypo-amino-acidemia of pregnancy may be due to this function of the placenta, although other factors such as renal loss of amino acid may contribute to the lower maternal levels. Our data, which fail to show an effect of estrogen or progesterone on amino nitrogen concentration during the early puerperium, are consistent with this concept. It seems unlikely that the endocrine factors studied are responsible for the gestational changes in amino nitrogen concentration.

Summary

1. Administration of estrogenic material, with or without progesterone, to patients in the early puerperium did not influence the normal postpartum rise in amino nitrogen.

2. Although other factors may be involved, these observations are consistent with the concept that the hypo-amino-acidemia of pregnancy is based on active placental transfer of amino acids from the maternal circulation.

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THE TREATMENT OF THREATENED AND RECURRENT ABORTION: A CRITICAL REVIEW

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THE management of abortion, both threatened and recurrent, remains one of the major unsolved problems in the field of gynecology. The literature on this subject abounds with a diversity of opinion, not only in respect to therapy, but even as to the basic statistics of these disorders. It has become evident in recent years that part of this confusion is due to the fact that patients with threatened or recurrent abortion comprise heterogeneous groups, in which the disorders may be influenced by a number of factors, largely unknown. Statistics on such a mixed population are apt to be highly misleading and the breakdown of clinical material into homogeneous subgroups appears to be essential for further progress. Thirteen years have elapsed since the careful review of Hertig and Livingstone[1]; a search of the more recent literature indicates that considerable new information has accumulated but that only a small fraction of the data have been presented or examined in such a fashion as to be statistically meaningful. King[2] in 1953 was the first to apply any sort of a statistical evaluation to the published figures. Indeed, it is distressing to compare the quality of experimental design and statistical interpretation which are considered a bare minimum in other fields of biological research with the general caliber of material considered acceptable for publication in the field of threatened and recurrent abortion. Good experimental design requires the incorporation of proper controls, yet it is surprising how many studies, both past and recent, have substituted for these controls a comparison with the results obtained by others, who may or may not have had a material homogeneous with that of the current investigator. Even more dubious is the substitution of a theoretically derived calculation of the frequency of expected abortion for an actual control group. Despite the obvious hazards of such a procedure, enough reports have relied on the mathematically simple but medically naive calculation of Malpas[3] to warrant further comment.

This calculation, based on the premise that a certain percentage of recurrent abortions are due to a single constant and persistent cause, attempts to predict the outcome of successive pregnancies after increasing numbers of abortions. Depending on the numbers used for the total incidence of spontaneous abortions and for the incidence of recurrent abortions, various prediction percentages may

be derived. For example, it may be calculated that, after two abortions, 13 to 22 per cent of third pregnancies will be aborted; after three abortions, about 38 per cent will be aborted, and so on. Malpas[3] claimed to find objective support for his calculations in the earlier data of Whitehouse. For some reason this assertion was not examined critically until Guterman[4] pointed out inherent fallacies both in the premise and in the data supposedly corroborating the calculation. More recently, Speert[5] also commented on this problem and suggested that the data on incidence necessary for the interpretation of Malpas' formula are not only unavailable but may actually be unobtainable for statistical reasons.

TABLE I. RECENT STUDIES OF RECURRENT ABORTION

AUTHOR	% OF PREGNANCIES ABORTED AFTER 2 PREVIOUS PREGNANCIES	3 PREVIOUS PREGNANCIES	4 PREVIOUS PREGNANCIES	OVER 4 PREVIOUS PREGNANCIES
A. Primary (Consecutive) Recurrent Abortion				
Theorized.—				
(Malpas, Eastman-Malpas)	13-22	38	73-84	94
Observed.—				
Alder[6]	30 (90)*			
Bevis[7]		20 (15)	20 (5)	0 (3)
Colvin et al.[8]	23 (141)†			
Guterman[4]	6 (32)	25 (20)	67 (3)	0 (2)
Jones and Delfs[9]	26 (23)	39 (28)	50 (16)	57 (14)
Robson & Gornall[10]		20 (5)		
Schoeneck[11]	44 (?)	0 (9)		
Speert[5]		19 (37)	33 (24)	33 (15)
Rucker[12]		17 (?)		
Total number of patients‡	286	114	48	34
Range of abortion frequency (%)	6-44	0-39	20-67	0-57
Average abortion frequency (%)‡	**23.4**	**23.7**	**39.6**	**38.2**
B. Secondary (Nonconsecutive) Recurrent Abortion				
Bevis[7]		25 (4)	33 (3)	0 (2)
Guterman[4]	10 (13)*	30 (14)	17 (6)	–
Jones and Delfs[9]	78 (9)	8 (13)	0 (2)	100 (1)
Randall et al.[13]			27 (?)	
Speert[5]	–	0 (29)	22 (9)	14 (7)
Total number of patients‡	22	60	20	10
Range of abortion frequency (%)	10-78	0-30	0-33	0-100
Average abortion frequency (%)‡	**36.4**	**10.0**	**20.0**	**20.0**

*Number in parentheses indicates number of patients.
†Number with 3 or more consecutive abortions not segregated in publication.
‡Reports not specifying the number of patients are omitted from calculation.

Instead of reviewing these arguments in further detail, it may be more profitable to examine some recent and statistically more acceptable studies of recurrent abortion (Table I, *A*). It is quite evident, even from this incomplete tabulation, that the facts do not support the hypothesis of Malpas and suggest (as indeed should have been obvious from the outset) that it represents a great oversimplification of the problem. One may also conclude, from the wide range of abortion frequencies, that the published clinical material is quite heterogeneous and that individual control groups must be used by investigators, as emphasized years ago by Guterman.[4] It seems probable, also, that

limitation of study material to patients who have had three (rather than two) consecutive abortions is an unnecessarily severe restriction which has been based on a tacit acceptance of Malpas' formula. If anything, there is a sharp rise in the frequency of abortion after *four* consecutive abortions, but unfortunately the number of patients reported in this and higher groups is very limited.

One statistical error which ignores even the basic premise of Malpas is the use of patients with recurrent abortion whose abortions have not been consecutive. Malpas specified a persistent and recurring abortifacient factor and therefore implied consecutive abortions; the difference in prognosis when the abortions are not consecutive is clearly shown in Table I, *B*). A further refinement of this concept has been the definition of "primary" recurrent abortion—in which the patient has *never* had a term pregnancy—as contrasted to one who has had a number of consecutive abortions. It would be most valuable if future students of this field were to classify their clinical material with these concepts in mind. At the present time it is often impossible to assess the published data.

Tacit acceptance of Malpas' idea of a progressively increasing incidence of abortion has led to some serious errors in the interpretation of therapeutic results, even in the recent literature. It is attractive, for example, to present a group of recurrent abortion patients with a previous abortion frequency of x per cent, predict what the outcome of the succeeding pregnancies should be (or assume that it will at any rate be worse than it was before) and then compare the therapeutic results with this *purely hypothetical prediction*. The fallacy of this reasoning is of course apparent, and has been amply verified in a study of 198 patients by Lloyd.[16] This group of women had a previous history of 691 pregnancies with an abortion rate of 88 per cent. Routine preconceptional measures were taken and urine specimens collected for study; no hormone therapy of any kind was given. In the following 115 pregnancies, the abortion rate was 28 per cent. (Note the good agreement of this figure with the average abortion frequencies in Table I, *A*.) In the light of these facts, it is necessary to re-examine the conclusions of Davis and Fugo,[14] who reported a 33 per cent abortion rate after progesterone therapy and considered this a highly successful result when compared with the abortion rate which might be expected from Malpas' calculation. Reifenstein[15] more recently used the same approach, which he characterized as "each woman serving as her own control." He, too, thought that his abortion rate of 32.5 per cent after progesterone therapy was a meaningful improvement over the previous abortion rate of 87.3 per cent in this same group. That such a result could occur without progesterone therapy is evident from the data of Table I, *A*. In this tabulation there were 286 patients with a 100 per cent previous abortion rate for two pregnancies and 114 patients with a 100 per cent abortion rate for three previous pregnancies, yet the abortion rates in the succeeding pregnancies were only 23.4 per cent and 23.7 per cent, respectively (without progesterone therapy, of course). It is therefore clear that the efficacy of therapeutic

measures cannot be evaluated by this type of approach; indeed, no amount of mathematical maneuvering can substitute for a proper experimental design such as the standard "double-blind" study.

It will be noted that the data presented in Table I and succeeding tables are expressed as abortion rates or frequencies, instead of "salvage rates," a more common term. Since the very term "salvage" implies the desired result whose achievement is in question or under investigation, its use can be ascribed only to wishful thinking, a desire to avoid the unpleasant realities of the situation, or perhaps to subliminal salesmanship. It is reminiscent of Ambrose Bierce's famous definition of gravitation: "the tendency of all bodies to approach one another with a strength proportioned to the quantity of matter they contain—the quantity of matter they contain being ascertained by the strength of their tendency to approach one another. This is a lovely and edifying illustration of how science, having made A the proof of B, makes B the proof of A."

Importance of Endocrine Studies in Abortion

In view of the complex endocrine equilibrium which is involved in the process of gestation, it would seem profitable to explore abnormalities of the endocrine system as factors in the etiology of threatened and habitual abortion. Until very recently, however, this approach has been impeded by technical difficulties which are still very far from solved. It is a fact that the determination of estrogens has been little more than a crude estimate until the recent development of chromatographic techniques for the separation of urinary estrogens by Bauld[17] and others. To our knowledge these methods have not yet been applied to problems of threatened or habitual abortion. Until adequate methods such as these are employed, our quantitative knowledge of the estrogens in pregnancy must be considered primitive. What then of the *qualitative* aspects of estrogen metabolism? Two facts among many deserve mention. Recently, at least three new urinary estrogens have been discovered. Their significance is wholly unknown. Furthermore, it must be recalled that even the best methods for determination of estrogens, when applied to the urine, reveal only the nature and fate of that fraction of estrogen metabolites which appear at that site. It is thought that observations on this 60 to 80 per cent reflect what is going on in the organism as a whole, but support for this important assumption is far from adequate.

To a lesser degree, the same problems apply to progesterone. At the present time, methods are available for studying the numerous metabolites of progesterone separately or as a group. One is still faced with the problem that urinary pregnandiol represents only 10 to 20 per cent of endogenous progesterone, and Guterman has already given indication that the conversion of progesterone to pregnandiol may be altered in pathological states. Thus caution is indicated in the interpretation even of quantitative urinary steroid methods; bioassay methods, such as those relying on vaginal smears, have inherently a much greater error than chemical methods and must be interpreted with even greater reservations.

The changes in urinary chorionic gonadotropin excretion are so great in the course of pregnancy that valuable data have been obtained even with such rough techniques as serial-dilution frog tests, etc. Recently the methodology of precise bioassay has been developed by Loraine[18] and others and should provide a tool of great usefulness for the future.

The purpose of these remarks is not to belittle endocrine studies performed in the past, but to point out the need for further work with the improved techniques now available. As a matter of fact, much information can be gleaned from an examination of the available studies on the endocrine imbalances in recurrent and threatened abortion.

Endocrine Factors in Recurrent Abortion.—The importance of at least one endocrine abnormality in recurrent abortion is illustrated in Table II. The urinary pregnandiol excretion is such an important factor in the outcome of the pregnancy that even a basically inaccurate technique such as bioassay (Randall's vaginal smears are essentially that) can yield statistically significant results. Even when primary and secondary recurrent abortion are grouped together, as in the report of Schoeneck,[11] the difference between patients with normal pregnandiol excretion and those with low excretion is significant. By contrast, Wilson[19] drew rather far-reaching conclusions on the basis of 6 cases; classifying these according to the categories of Table II shows that they cannot be given much statistical weight.

TABLE II. CORRELATION OF ABORTION RATE AND URINARY PREGNANDIOL EXCRETION IN RECURRENT ABORTION

AUTHOR	ABORTION FREQUENCY (%)					
	PRIMARY		SECONDARY		MIXED, PRIMARY AND SECONDARY	
	NORMAL* URINARY PREGNANDIOL	LOW URINARY PREGNANDIOL	NORMAL URINARY PREGNANDIOL	LOW URINARY PREGNANDIOL	NORMAL URINARY PREGNANDIOL	LOW URINARY PREGNANDIOL
Guterman[4]	8% (?)†	100 (?)	–	27% (?)		
Randall et al.[13]‡	15 (41)	100 (49)§	8 (258)	27 (33)§		
Schoeneck[11]					8 (54)	57 (100)§
Wilson[19]	0 (1)	0 (1)	0 (2)			

*Normal is defined as 5 mg. per day or more of urinary pregnandiol; "low" as less than 5 mg. per day.

†Number in parentheses indicates number of patients.

‡Except for these statistics, primary and secondary recurrent abortion is defined as indicated in the text. Randall defines "poor obstetrical history" (grouped under primary) as abortion of two-thirds or more of previous pregnancies, "good obstetrical history" (grouped as secondary) as term outcome of two-thirds or more of previous pregnancies. The number, 49, in the low-pregnandiol primary abortions indicates 49 *pregnancies* in 10 patients.

§The difference between "normal" and "low" groups is statistically significant at the 1 per cent level or lower.

TABLE III. UNTREATED THREATENED ABORTION

AUTHOR	ABORTION FREQUENCY (%)
Various, prior to 1944 (review of Hertig and Livingstone[1])	34.3 (274)*
Colvin et al.[8]	28 (1,570)
Crowder[20]	43 (37)
Falls[21]	55-60 (?)
Kotz[22]	38 (45)
Total number of patients	1,926
Range of abortion frequency (%)	28-60
Average abortion frequency (%)	29.4

*Number in parenthesis indicates number of patients.

Endocrine Factors in Threatened Abortion.—Before considering endocrine factors in threatened abortion, some note should be taken of the range of figures reported even in *untreated* threatened abortion (Table III). Colvin,[8]

for example, stated that 28 per cent of a large group of patients aborted, whereas Falls[21] reported an abortion rate of 55 per cent in an unspecified number of cases.

As early as 1939, Browne, Henry, and Venning[23] noted that a diminished pregnandiol excretion was associated with eventual abortion, and these findings have been confirmed and extended by Cope,[24] Hain,[25] and many others. More recently Guterman and Tulsky[26] have reviewed the problem in numbers of patients on the basis of urinary pregnandiol determinations. Randall[13] has studied the problem by reliance on the vaginal smear as an index of progesterone production. The results of these and other studies are summarized in Table IV, and show clearly the difference in the prognosis of threatened abortion with normal versus persistently low levels of pregnandiol excretion. It must be pointed out, however, that low pregnandiol excretion cannot be equated with a tendency toward abortion, for it has been observed that from 7 to 12 per cent of uneventful pregnancies also show low levels of pregnandiol excretion. One also finds, of course, that patients with normal pregnandiol excretion threaten and eventually go on to abortion. Obviously, a low pregnandiol excretion is not the only important factor predisposing to threatened abortion, for in Koff and Tulsky's[32] series only 42 per cent of the patients with threatened abortion had low pregnandiol excretion, and in Randall's[13] series there was evidence of progesterone deficiency from the vaginal smear in only 38 per cent of the cases of spontaneous abortion. It is clear, however, that low pregnandiol excretion *in a patient with threatened abortion* is a complication with a very serious prognosis.

TABLE IV. CORRELATION OF ABORTION RATE AND URINARY PREGNANDIOL EXCRETION IN THREATENED ABORTION

AUTHOR	ABORTION RATE (%)	
	NORMAL PREGNANDIOL*	LOW PREGNANDIOL
Baker et al.[27]	12 (25)	17 (6)
Bender[28, 29]	23 (22)	83 (6)
Borglin[30]	21 (58)	89 (44)
Guterman[4]	14 (77)	90 (71)
Guterman and Tulsky[26]	23 (104)	97 (106)
Randall et al.[13]	7.5 (?)	51 (?)
Robson and Gornall[10]	39 (23)	94 (17)
Swyer[31]	36 (22)	83 (18)
Total number of patients	331	268
Range of abortion frequency (%)	7.5-39	17-97
Average abortion frequency (%)	21.8	90.7

*Over 5 mg. per day.

Assessment of Therapeutic Effectiveness

In the light of these findings it becomes apparent that the assessment of any therapy of recurrent or threatened abortion which does not take into account the primary or secondary nature of recurrent abortion, and the urinary pregnandiol excretion in both disorders, is fraught with difficulty. Any treatment applied to a group of patients *who will abort less than one third of the time even if left alone* will look promising unless a simultaneous control group is available for comparison; by the same token, the true efficacy of a treatment is difficult to demonstrate. If, however, a given form of treatment is evaluated in patients with a low pregnandiol excretion, where an abortion rate from 80 to 100 per cent may be expected without treatment, the likelihood of observing a statistically meaningful effect is proportionately

greater. By means of a common statistical technique, the chi-square test, it is possible to calculate the number of patients required in a therapeutic trial to bring a given level of response out of the realm of chance occurrence. This is illustrated in Table V. If, for example, the abortion frequency in untreated patients is 26 per cent, and this figure is obtained from a study of 50 controls, an abortion rate of 12 per cent in a group of 50 treated patients is still likely to have occurred by chance alone 5 per cent of the time ($p = > 0.05$). It is not until the abortion frequency drops to 10 per cent in the treated group that statistical significance is achieved, and this answer has required the study of 100 patients. If, however, one chooses to select a group of patients in whom a study of 20 untreated patients yields a 90 per cent abortion rate, the therapeutic evaluation becomes much more simple. If the abortion rate in the treated group falls only to 50 per cent, it will require only a group of 20 patients to confirm the point; as a matter of fact, groups of only 15 controls and 15 treated patients come very close to statistical acceptability ($p = .02$). Control and treatment groups of only 10 patients each will not yield statistically meaningful results even though the abortion rate in the treated group falls to 10 per cent (p is still only .07). This is of course an oversimplified statement of the problem and it is assumed that the customary requirements of a proper randomized design have been met. On this basis, however, one may examine and evaluate published results of the effect of various forms of therapy.

TABLE V. EXAMPLES OF THE USE OF THE CHI-SQUARE TEST IN DETERMINING WHETHER A PARTICULAR EXPERIMENTAL GROUPING CAN YIELD A STATISTICALLY MEANINGFUL ANSWER

CONTROL		TREATED		
NO. OF PATIENTS	ABORTION RATE (%)	NO. OF PATIENTS	ABORTION RATE (%)	STATISTICAL SIGNIFICANCE
50	26	50	12	$p = > .05$
50	26	50	10	$p = < .01$
20	90	20	50	$p = < .01$
15	90	15	50	$p = .02$
10	90	10	50	$p = .28$
10	90	10	10	$p = .07$

The effects of various nonendocrine treatments are shown in Table VI, *A*, and for comparison two series (Guterman, Jones and Delfs) are included in which therapy was withheld. It is hardly surprising that the abortion frequencies with various therapies and in heterogeneous groups of patients with recurrent abortion should range from 19 to 70 per cent. As a consequence, the calculated *average* abortion frequency (36.7 per cent) has a very limited significance.

The excellent results (a 19 per cent abortion rate) achieved by Bevis in 32 patients with no treatment other than the psychotherapeutic impact of an intensive diagnostic survey warrant close attention. Statistical comparison by the chi-square test shows that the results of Javert, either with "various" forms of therapy or with his complex 14 point program of "current therapy" in groups of 41 and 35 patients, respectively, are no better than those achieved by Bevis with no therapy at all. The statistical difference between the results of Bevis and the best results of Javert is only $p = 0.10$. The preconceptional regime of Hughes and co-workers is associated with a comparable abortion frequency.

Several reports on the trial of stilbestrol in recurrent abortion are summarized in Table VI, *B*. Again, there is recorded a wide range of abortion

TABLE VI. EFFECT OF THERAPY IN RECURRENT ABORTION

AUTHOR	TREATMENT	TYPE OF RECURRENT ABORTION: MIXED (ABORTION FREQUENCY, %)	PRIMARY (ABORTION FREQUENCY, %)	SECONDARY (ABORTION FREQUENCY, %)
	A. Nonendocrine Therapy			
Guterman[4]	None		89 (9)*	
Jones and Delfs[9]	None	70 (33)		
Bevis[7]	Psychotherapy	19 (32)		
Various prior to 1944[1]	Vitamins, etc.	35 (81)†		
Hughes[34]	Preconceptional	20 (50)†		
Javert[33]	Various		15 (41)	0 (7)
	"Current therapy"		6 (35)	0 (8)
Rutherford[35]	Progesterone in homeopathic doses	44 (63)		
Total number of patients		259	85	15
Range of abortion frequency (%)		19-70	6-89	–
Average abortion frequency (%)		**36.7**	**18.8**	**0**
	B. Stilbestrol Therapy			
Davis and Fugo[14]		55 (38)		
Grant[36]		47 (?)		
Plate[37]		29 (31)	29 (7)	14 (7)
Rosenblum and Melinkoff[38]		50 (10)		
Smith and Smith[39]		15 (48)‡		
		43 (33)§		
Total number of patients		160	7	7
Range of abortion frequency (%)		15-55	–	–
Average abortion frequency (%)		**35.0**	(29)	(14)
	C. Progesterone Therapy			
Various[1]	Various levels	15 (40)		
Bishop and Richards[40]	Implant	31 (32)		
Bishop, Richards, and Doll[41]	Implant		17 (12)	0 (4)
Davis and Fugo[14]	50 mg./day	33 (18)		
Davis and Plotz[42]	300-500 mg./wk.	34 (79)		
Grant[36]	Pellets	28 (?)		
Guterman[4]	50-100 mg./day		29 (7)‖	
Jones and Delfs[9]	25 mg. intramuscularly or 150 orally/day	15 (41)		
Kamal[43]	Implant	33 (15)		
	Inj. crystals	17 (29)		
Karim and Wahba[44]	40 mg. intravenously 3 times	27 (11)		
Kupperman and Epstein[45]	Oral progesterone 1,000 mg./day¶	17.4 (47)		
Reifenstein group[15]	P caproate		38 (53)	31 (91)
Robson and Gornall[10]	20-30 mg./day	25 (4)		
Rosenblum and Melinkoff[38]		71 (7)		
Vaux and Rakoff[46]	20 mg./week	0 (11)		
	Estrogen also	33 (24)		
Total number of patients		358	72	95
Range of abortion frequency (%)		0-33	17-38	0-31
Average abortion frequency (%)		**25.1**	**33.4**	**28.4**

*Patients with primary abortion who were threatening to abort. See Part B.

†Defined as 2 or more consecutive abortions.

‡Three consecutive abortions.

§More than 3 consecutive abortions.

‖Patients with primary abortion who were threatening to abort. Difference from comparable untreated group of Part A is possibly significant ($p = 0.05$).

¶Unpublished results.

frequencies after treatment. However, the 259 patients of Table VI, *A*, who received no hormone therapy, and the 160 stilbestrol-treated patients in Table VI, *B* are sufficiently large groups to permit a tentative comparison. The average abortion frequencies of the two groups—36.7 and 35.0 per cent, respectively—are statistically identical. It must be emphasized, nevertheless, that the nonuniformity of the assembled clinical material may well be such as to disguise real differences between the groups. It is most unfortunate that there are not sufficient data on primary recurrent abortion in patients with low pregnandiol levels treated with stilbestrol to permit a comparison with appropriate controls.

Table VI, *C* summarizes the findings of a considerable number of workers who administered progesterone in a variety of forms and dosages. Except for the 11 cases of Vaux and Rakoff in which total salvage was observed, the abortion incidence ranges fairly consistently between 15 and 33 per cent. The average abortion frequency for the aggregate 358 patients is 25.1 per cent. There is obviously no difference between this incidence and the 23.4 per cent frequency of abortion observed in patients who have had two consecutive abortions and received no hormone therapy (Table I, *A*). This is far more significant than a comparison with the abortion rate in patients treated with nonendocrine means (36.7 per cent, Table VI, *A*). At first glance, progesterone treatment would seem to offer significantly better results than the nonendocrine treatment; the true interpretation, of course, is that the clinical material is not homogeneous and that the average abortion rate of the reports in Table VI, *A* happened to be worse than that of the untreated population of Table I, *A*. This merely emphasizes the difficulties of statistical interpretation when investigators do not incorporate proper controls into their experiments. To date, therefore, an over-all examination of the results of progesterone therapy (of all kinds) in recurrent abortion (a mixed group of patients) fails to disclose evidence of any benefit. Even the comparison of over-all results of progesterone therapy in primary or secondary recurrent abortion with comparable data of Table I, *A* is probably not meaningful, since the range of reported abortion frequencies is so great. A more valid comparison may be made between the untreated group of 9 patients with primary recurrent abortion showing an abortion frequency of 89 per cent (Table I, *A*) and the 7 similar patients treated with progesterone (Table VI, *C*) as reported by Guterman. In spite of the low abortion frequency of 29 per cent in the treated group, the numbers of patients are so small that the statistical difference is not significant. The unpublished studies of Kupperman and Epstein[45] are probably the most important recent contribution to the problem of progesterone therapy in recurrent abortion, since the clinical material was confined to patients with three or more abortions *in whom the pregnandiol excretion was low* for the particular stage of pregnancy. From Table II it may be seen that the abortion rate in such patients approaches 100 per cent without treatment. In 47 patients who received 1,000 mg. of progesterone orally per day in whom the study was completed at the time of this writing, the abortion rate was only 17.4 per cent, a highly significant difference from the appropriate control observations. Except for this report, there is at the present time no published unequivocal proof of the effectiveness of progesterone therapy even in patients with primary recurrent abortion. It is most probable that a large number of patients whose abortion classification and urinary pregnandiol excretion were known have been treated with substantial doses of progesterone over prolonged periods; unfortunately, the publications dealing with this problem have all too often neglected to include an adequate tabulation of the clinical material from this point of view.

TABLE VII. EFFECT OF STILBESTROL THERAPY IN THREATENED ABORTION

AUTHOR	ABORTION FREQUENCY (%)
Crowder[47]	49 (63)
Grant[36]	"Same as bed rest" (90)
Rosenblum and Melinkoff[38]	13 (81)
Smith[48]	22 (191)
Total number of patients	335
Range of abortion frequency (%)	13-49
Average abortion frequency (%)	24.8

TABLE VIII. EFFECT OF PROGESTERONE THERAPY IN THREATENED ABORTION

AUTHOR	TREATMENT	ABORTION FREQUENCY (%)		
		URINARY PREGNANDIOL NOT STATED	URINARY PREGNANDIOL NORMAL	URINARY PREGNANDIOL LOW
Various (prior to 1944)[1]	Various	40.5		
Baker et al.[27]	100 mg./day		0 (18)	0 (6)
Bender[28, 29]			50 (6)	25 (4)
Falls[21]	Not stated	20 (?)		
Guterman[4]			10 (9)	17 (12)
Guterman and Tulsky[26]	5-20 mg./day		18 (87)	97 (38)
	100 mg./day			70 (27)
Hertig and Livingstone[1]	Small doses	20 (?)		
Hudson and Rucker[49]	Small doses	57 (68)		
Karim and Wahba[44]	40 mg. intravenously	18 (41)		
Kotz[22]	Small doses	35 (184)		
Rosenblum and Melinkoff[38]		35 (86)		
Total number of patients		379	120	87
Range of abortion frequency (%)		18-57	0-50	0-97
Average abortion frequency (%)		37.2	16.7	67.8

An evaluation of therapy in *threatened* abortion is presented in Tables VII and VIII. In a large number of patients with threatened abortion (pregnandiol excretion not specified), the abortion frequency averaged 29.4 per cent, with a range of 28 to 60 per cent (Table III). Most clinical trials have not distinguished between patients with normal and low pregnandiol excretion. The interpretation of results therefore depends on the assumption that chance will adequately distribute the proportions of these two types. If the prognosis of the two groups were similar, this assumption would be of little consequence, but as the evidence of Table IV indicates, this is not the case. There is an average abortion rate of only 21.8 per cent in the normal-pregnandiol group, compared to a 90.7 per cent abortion rate in the low-pregnandiol group, without treatment. Therapeutic trials in mixed populations (unless the numbers are very large) must consequently be interpreted with great caution.

Stilbestrol therapy (Table VII) has been accompanied by abortion frequencies ranging from 13 to 49 per cent, with an average frequency of 24.8 per cent. This average does not differ statistically ($p = 0.09$) from the 29.4 per cent abortion rate of 1,926 patients who received no hormone therapy (Table III). This is the same conclusion as that of Grant,[36] who stated that the results in 90 patients were the same as achieved by bed rest; unfortunately the latter data are not presented in a fashion suitable for statistical evaluation. No reports have been found on the effect of stilbestrol therapy on patients threatening to abort who have been shown to have a low urinary pregnandiol excretion by acceptable methods.

The published results of progesterone therapy in threatened abortion are summarized in Table VIII. A range of abortion frequencies varying from 18 to 57 per cent has been reported following such treatment. The average abortion frequency, based on a total of 379 patients, is 37.2 per cent, which is significantly different ($p = < 0.01$) from the average of 29.4 per cent in 1,926 patients who did not receive hormone therapy. Falls[21] has stated that his abortion frequency prior to progesterone therapy was about 55 to 60 per cent, that it dropped to 20 per cent when subsequent patients were given progesterone, and that it rose once again to the original level when the use of progesterone was discontinued. A total of about 400 patients were said to have been involved in this study. It is most unfortunate that Falls gave no exact figures, thus making it impossible to interpret the results of a study with a good experimental design. One must also note that the control abortion rate reported by Falls is much higher than any quoted by other investigators.

From Table IV it may be seen that the abortion frequency in patients with normal urinary pregnandiol who threaten to abort averages 21.8 per cent, with a range from 7.5 to 39 per cent. With such a low abortion rate, based on a total of 331 patients, it is apparent that the effectiveness of almost any form of therapy will be very difficult to demonstrate just from purely statistical considerations. In point of fact, 120 such patients have been treated with progesterone in varying amounts, and the abortion frequency in the treated patients has an average of 16.7 per cent, with a range from zero to 50 per cent. One can only conclude that it has not been possible to demonstrate any effect of progesterone treatment in this group of patients.

In patients with threatened abortion who have a low pregnandiol excretion, the circumstances are more favorable for the demonstration of possible therapeutic benefits. Table VIII indicates (in a total of 87 patients) that the abortion frequency varies from zero to 97 per cent when progesterone is administered. Even with this wide range, the salvage rate is significantly better than that observed without progesterone treatment. A better evaluation of these findings is possible, however. It may be noted that the best results (zero and 25 per cent abortion rates) stem from exceedingly small series; even so, 6 treated patients with no abortions have statistical weight when compared to 268 patients with a 90.7 per cent abortion rate. The worst results are those reported by Guterman and Tulsky in cases where 5 to 20 mg. progesterone were given daily. At the present time, this would be considered inadequate dosage and the poor results are therefore not meaningful. On the other hand, when the same workers raised the treatment level to 100 mg. per day in 27 patients, the abortion rate was 70 per cent, compared to their own control group of 106 patients (Table IV) with an abortion rate of 97 per cent. This difference is highly significant (p is much less than 0.01) and in view of the fact that the control and treated groups were part of the same investigation, these results assume added significance. It may be concluded with considerable assurance, therefore, that high-dosage progesterone therapy is of significant benefit in patients with a low urinary pregnandiol excretion who are threatening to abort.

A further endocrine aspect deserves mention. Delfs and Jones have reported upon 18 patients with low chorionic gonadotropin excretion, all of whom subsequently aborted. Whether this finding was merely a feature of the impending abortion, whether it was a contributing complication just as low pregnandiol excretion seems to be, or whether it is causally related remains a problem for further investigation. Hughes and many others have also observed these low chorionic gonadotropin levels in a significant number of patients. In view of studies such as those of Segaloff and others,[50] which

showed that very large doses of chorionic gonadotropin (of the order of 5,000 I.U. per day) are necessary to prolong the life of the normal corpus luteum, it may well be that therapeutic efforts with this hormone in various forms of abortion may have to be re-evaluated at much higher dose levels.

Summary

It is apparent that there is a considerable diversity of opinion, not to say confusion, as to the nature and proper treatment of threatened and recurrent abortion. One important factor in this confusion is the obvious heterogeneity of these classifications, and this difficulty is compounded by the reluctance of many clinicians to include proper controls (i.e., untreated patients) in their studies.

From this review there also emerge the following conclusions:

1. The abortion frequencies predicted by the Malpas formula do not conform to the observed facts; hence the substitution of this prediction for a control group of patients vitiates the subsequent conclusions.

2. Restricting the term "recurrent" or "habitual" abortion to three rather than two consecutive abortions has no statistical justification. It is only after four consecutive abortions that the subsequent abortion rate changes appreciably.

3. The prognosis in *recurrent abortion* is markedly influenced by the past obstetrical history ("primary" or "secondary" abortion) and by the urinary pregnandiol excretion. For investigative purposes patients should be classified at least with respect to these two criteria.

4. In the treatment of recurrent abortion, psychotherapeutic influences appear to be just as successful as the most complex medical regimes, such as that of Javert. The abortion rate in patients who receive stilbestrol is not significantly lower than the rate in patients who receive no hormones at all. Recent evidence indicates that massive progesterone therapy may be of value in patients with recurrent abortion who have low urinary pregnandiol excretion.

5. In *threatened abortion,* the prognostic significance of a low pregnandiol excretion is very grave. There is no statistical evidence for the value of stilbestrol therapy. There is definite evidence, as well as some inconclusive reports, of benefit from progesterone therapy. Particularly in the case of patients with low pregnandiol excretion, the benefit of progesterone therapy seems to be statistically valid.

Some problems in the statistical design of experiments in this field have been discussed, together with an illustration of the application of the chi-square method for determining the feasibility of proposed clinical investigations.

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THE ELECTRONIC EVALUATION OF THE FETAL HEART RATE*

Preliminary Report

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SINCE Cremer[1] reported the first successful recording of a fetal electrocardiogram in 1906, a number of reports of fetal electrocardiography have appeared in the medical literature. By and large, fetal electrocardiography has been used for the diagnosis of fetal life.[2-14] More recently, attempts have been made to correlate changes in fetal ECG configuration with abnormal fetal environment.[15]

The purpose of this paper is to report the use of recently developed electronic techniques for evaluation of the instantaneous fetal heart rate throughout labor and delivery. The possible mechanisms of "physiologic" and "pathologic" fetal bradycardia will also be discussed.

While fetal bradycardia and cardiac irregularities are considered clinical signs of fetal distress, it is quite obvious that periodic auscultatory sampling of the fetal heart rate in the interval between contractions is relatively inaccurate.

To determine more definitively the probable human error in counting fetal heartbeats, a number of pulses of known rate were put on magnetic tape and 15 obstetricians were asked to count the several rates and record them. Fig. 1 is a graph of the range of counts from this experiment and shows the maximum error at rates slower and faster than normal.

With electronic techniques this type of error can be avoided, and at the same time means provided for correlating accurately uterine activity with changes in the fetal heart rate.

Method

Eighty patients were studied with the fetal electrocardiograph throughout labor or the portion of labor after clinical signs of fetal distress had been noted. Included in this group were a number of "normal" labors. The total number of cases is too small to permit breakdown into specific groups, since a large number of variables has to be considered, e.g., age, parity, presentation, pelvis, status of membranes, etc. In addition to a description of the techniques used, the present observations are primarily concerned with the status of the newborn infant and the fetal heart rate pattern noted during that particular labor. For the purposes of this study, an infant was considered to show evidence of fetal distress if it had an Apgar score[16] of 5 or less.

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**Markle Scholar in Medical Science.

To date, uterine contractions have been determined clinically and their timing is subject to a certain amount of error which will be avoided by electronic techniques now being developed.

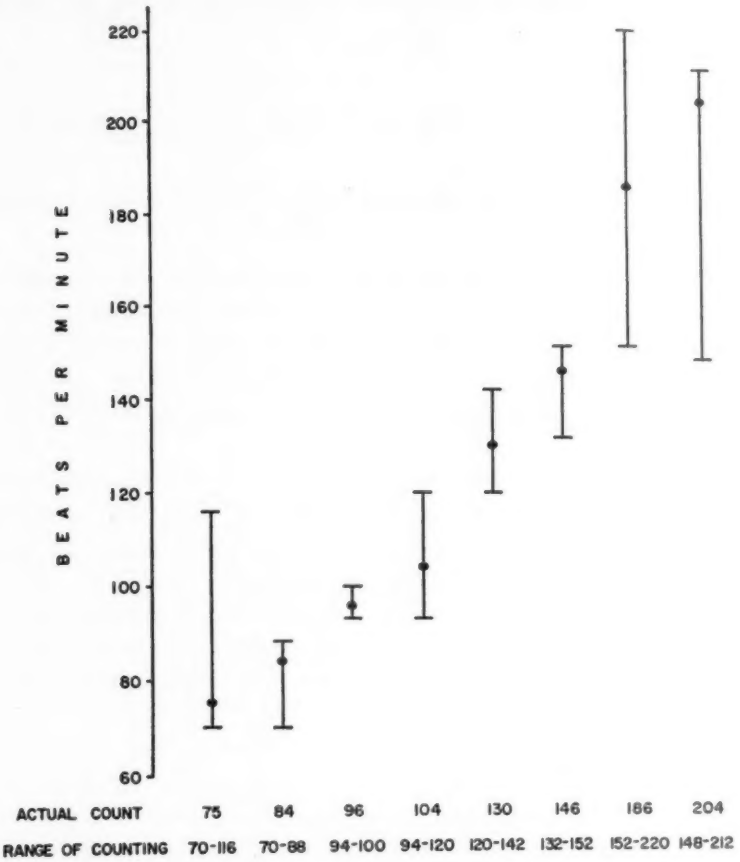


Fig. 1.—Range of error in counting simulated fetal heartbeats. The actual count is given on the line above the range obtained by auscultation.

Electrodes.—In order to reduce skin noise, light plastic shells which enclose a pure silver spiral electrode have been made. Contact with the patient's skin is made with a gauze wick which is wetted with saturated sodium chloride. The use of fluid-skin and fluid-electrode interfaces markedly reduces the extraneous noise due to skin movement. For short-term observation, the plastic shells are attached to the patient by small removable suction bulbs. For long labors the suction bulb is removed and the plastic shell cemented to the abdominal wall of the mother with Duco cement after the skin has been cleansed with acetone. The connecting leads are made of light shielded wire. The entire electrode assembly is comfortable and allows the mother to move as frequently as she wishes.

Positioning of Electrodes.—Bipolar electrodes are used to reduce the electrical interference usually present in the labor room. The ground electrode is placed on the thigh and the other two electrodes are usually placed in an epigastric-suprapubic midline or diagonal disposition. The final site is chosen to obtain maximum amplitude of the fetal ECG.

Preamplifier and Recording Systems.—Two systems are currently in use. The simpler of the two records both fetal and maternal electrocardiograms and the record has to be processed manually. The apparatus used with this system consists of a Tektronix 122 preamplifier* to whose input the electrodes are connected. The output of the preamplifier is coupled to an Elema 24 two-channel electrocardiograph.† A cathode-ray oscilloscope is also provided to aid in positioning of the electrodes so that a good fetal ECG may be obtained.

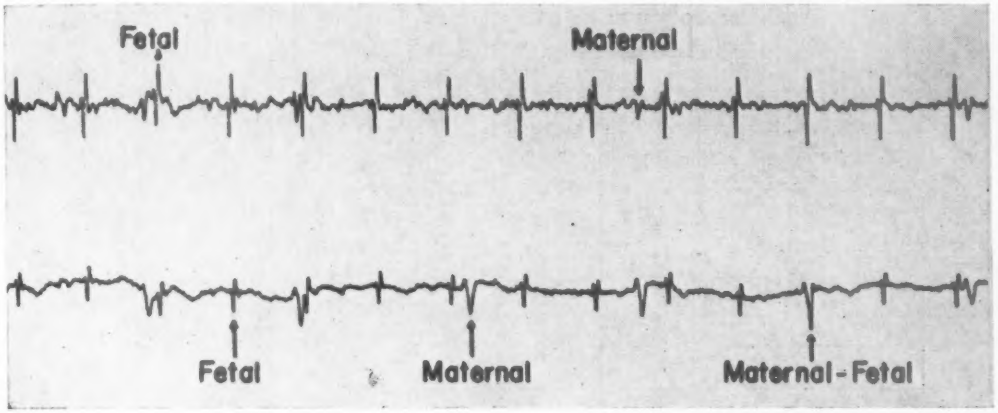


Fig. 2.—Separation of fetal and maternal electrocardiogram. The upper tracing shows attenuation of the maternal ECG and the separation of the fetal ECG for counting. The lower tracing shows the combined maternal and fetal ECGs as they are usually obtained from the mother's abdomen.

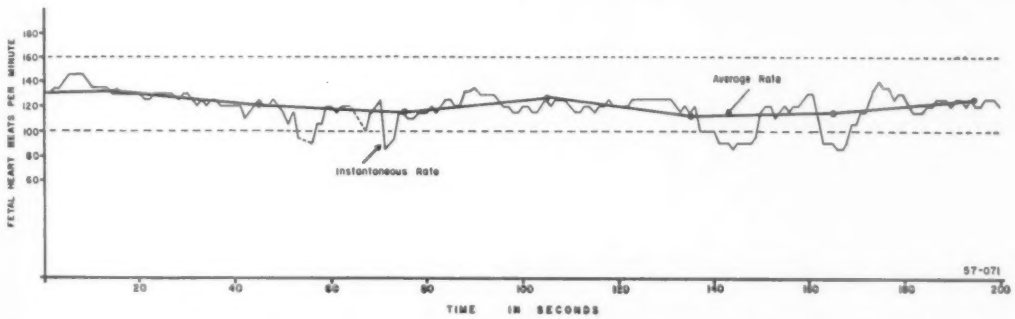


Fig. 3.—A comparison of average and instantaneous fetal heart rates during labor. The added detail available from the instantaneous rate is seen readily.

With manual data reduction methods, the entire tracing from the labor is marked off in 10 second segments. The fetal electrocardiograms and the intervals between them are scanned; if these are approximately equal, the time interval between two consecutive fetal ECGs occurring at the 10 second marker is measured and then converted to beats per minute. Thus in 1 hour of normal labor there are 360 time intervals to be determined and plotted. If gross variations in interval are noted in the 10 second segment, each time interval between consecutive fetal ECGs is plotted. (If it were necessary to plot all the time intervals in one hour of labor this would amount to about 9,000, assuming 150 beats per minute.) In practice, special plastic scales have been devised to minimize this work. For plotting a large number of time intervals a photoelectric cell system whose output feeds a cardiotachometer has been developed.

*Tektronix, Inc., Portland, Ore.
†Burdick Company, Milton, Wis.

Fig. 4.—Normal labor in a multipara without slowing of the fetal heart rate during uterine contractions. A relatively constant fetal heart rate throughout labor has been observed in nulliparas and multiparas with both breech and vertex presentations, and is therefore considered to be a normal pattern.

The second system has been previously described[17] and separates the fetal ECG from the maternal ECG by attenuation of the latter so that the fetal ECG alone is available for counting. Fig. 2 is a reproduction of a record showing attenuation of the maternal complex. The separated fetal ECG is used to trigger a cardiotachometer which plots the instantaneous rate and thus provides maximum data with much less effort than if manual data reduction is employed.

Observations

Average vs. Instantaneous Fetal Heart Rate.—Clinical auscultation of the fetal heart rate provides an average rate over a given period of time, usually 30 seconds. Fig. 3 is a diagram of the fetal heart rate during a portion of labor and demonstrates the loss of information when averaging techniques are used. The heavier curve is the average rate as determined every 30 seconds and the lighter curve shows the instantaneous rate as determined from beat to beat. The greater detail of the latter method is seen readily since it depicts the instantaneous variation of the fetal heart rate and therefore contains more information.

Fetal Heart Rate During Contractions.—No significant change in the fetal heart rate during contractions has been noted in breech presentations and in the majority of vertex presentations. In a small number of multiparous patients with vertex presentations the fetal heart rate may drop from 140 to 110-120 beats per minute at the height of a contraction and may return to normal 10 to 15 seconds before the contraction is over. Occasionally the rate may drop to less than 100 beats per minute at the height of a contraction. In the primigravid counterpart the same situation obtains, except that the drop in rate may be more pronounced. Instantaneous rates of 60-70 beats per minute have been noted with return to normal before the contraction is over.

Figs. 4 and 5 are graphs of the fetal heart rates throughout labor in two multiparas. Some detail has been lost in construction of the graphs but the data are substantially correct. Multiparous patients were chosen since their shorter labors permit convenient display of the total labor. The pattern of Fig. 4 is obtained in the majority of patients, that of Fig. 5 in the minority of vertex presentations; the frequency of occurrence of the latter being higher for primigravidas than for multiparas.

The Effect of Cervical Dilatation on the Fetal Heart Rate.—A short time after the inception of this study it appeared that the drop in the fetal heart rate noted with contractions was related to the degree of cervical dilatation present. In normal labor this was not noted before 4 cm. or after 8 cm. of dilatation. Initially, this was puzzling, since it was felt that the fetal bradycardia which occurs with contractions was due to compression of the placenta and consequent momentary anoxia. If this were so, it seemed reasonable that as labor progressed and the uterine contractions increased in amplitude and duration, fetal bradycardia would become more pronounced. Since this was not observed and fetal bradycardia began 10 to 15 seconds after the onset of a contraction and did not persist throughout the contraction, other mechanisms had to be considered. After additional study, it became apparent that fetal bradycardia, when present, was related to the degree of cervical dilatation. The possibility that fetal bradycardia might be related to increased intracranial pressure rather than to momentary anoxia following compression of the placenta was then explored. Before 4 cm. of dilatation the fetal skull is being forced against a relatively smooth cervix; as dilatation progresses more of the softer bones of the fetal skull are extruded through the enlarging cervical ring. When about 8 cm. of dilatation is reached the cervix is now impinging on the harder lateral areas

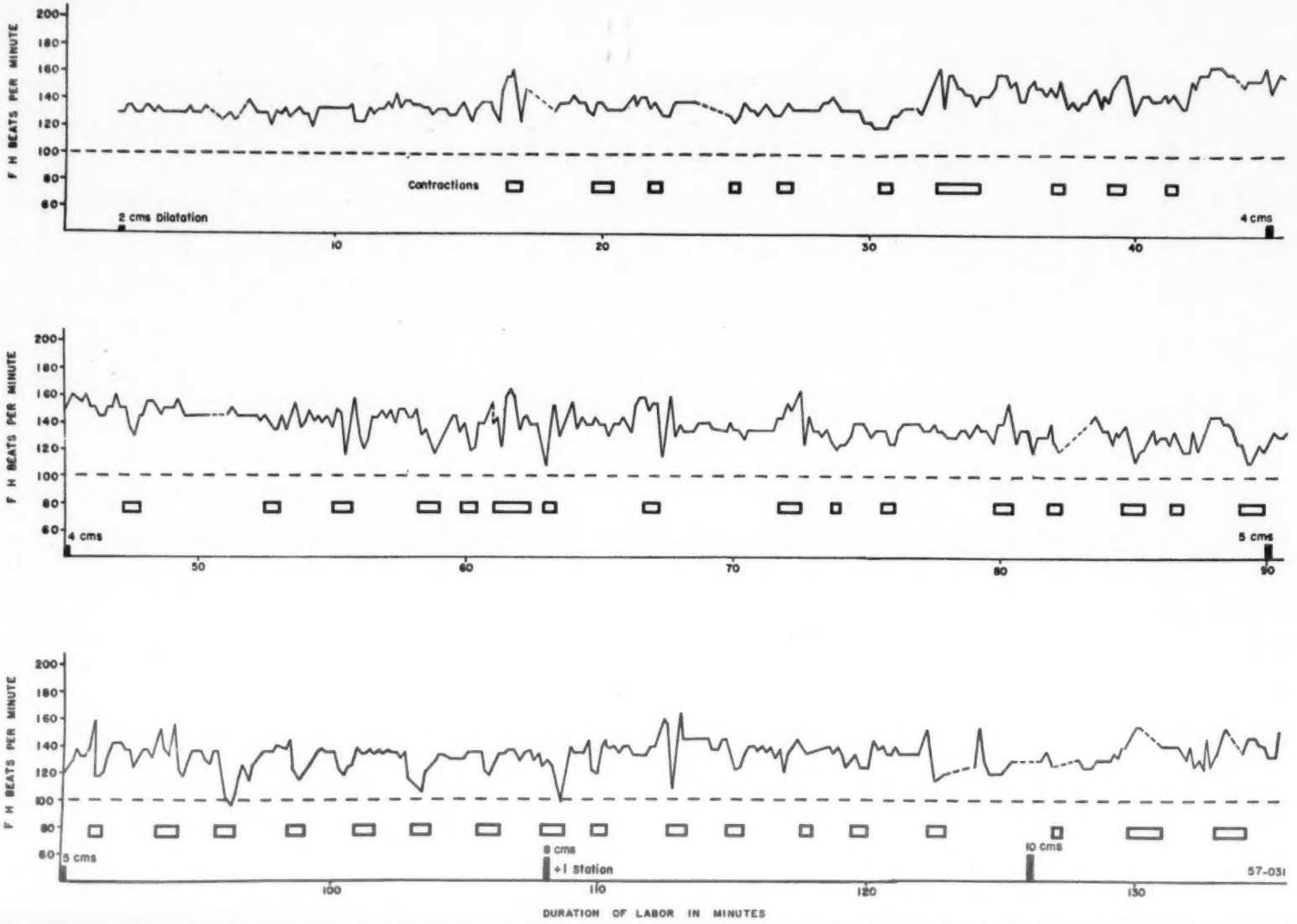
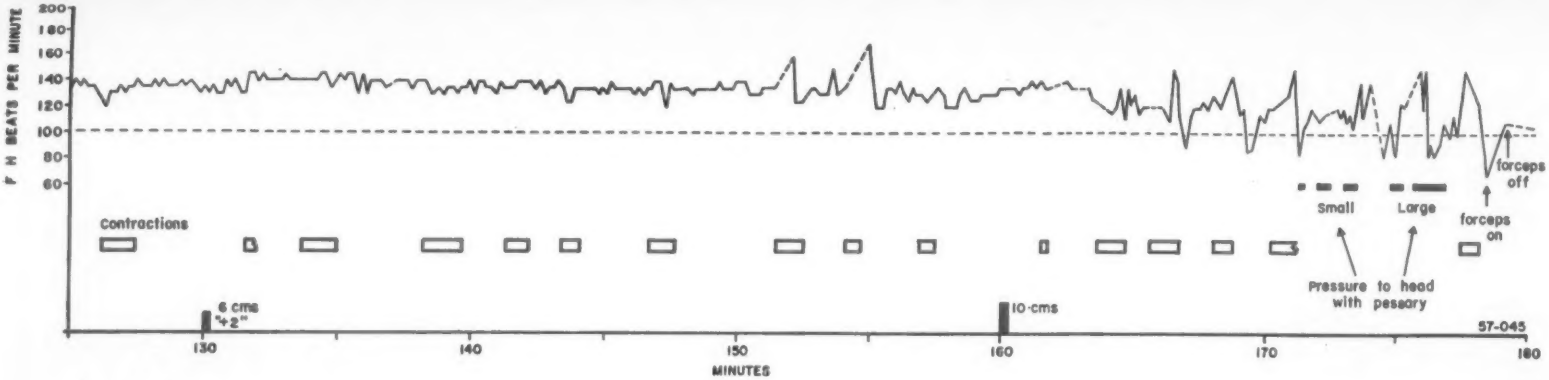


Fig. 5.—Normal labor in a multipara showing slowing of the fetal heart rate at the height of a uterine contraction. This is more commonly seen with nulliparous patients with vertex presentations between 4 and 8 cm. of dilatation. It is less commonly seen with multiparous patients and has not been noted in normal breech deliveries or in normal vertex deliveries before 4 cm. or after 8 cm. of dilatation.

DURATION OF LABOR IN MINUTES

Fig. 5.—Normal labor in a multipara showing slowing of the fetal heart rate at the height of a uterine contraction. This is more commonly seen with nulliparous patients with vertex presentations between 4 and 8 cm. of dilatation. It is less commonly seen with multiparous patients and has not been noted in normal breech deliveries or in normal vertex deliveries before 4 cm. or after 8 cm. of dilatation.



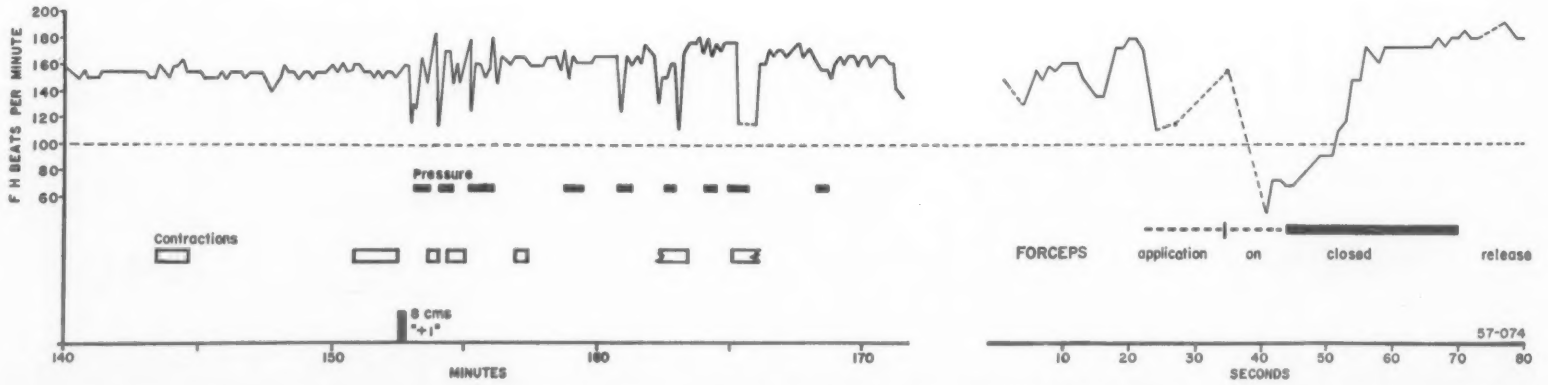


Fig. 6.—The effect of increased intracranial pressure on the fetal heart rate. The fetal bradycardia which is concomitant with contractions is thought to be largely a reflex response to increased intracranial pressure. The application of pressure to the fetal head with pessaries or forceps produces a similar type of bradycardia. In both the above instances no fetal bradycardia had been noted with contractions throughout the earlier labor, and it is therefore assumed that the bradycardia shown above is directly related to artificially produced increased intracranial pressure.

of the skull and the softer skull bones are once again being forced against a relatively smooth surface, this time the smooth superior aspect of the perineal floor. Bradycardia is again noted when the vertex is being extruded through the vaginal outlet.

The Effect of Increased Intracranial Pressure on the Fetal Heart Rate.—In an attempt to determine experimentally the effect of increased intracranial pressure, patients who had exhibited no drop in fetal heart rate with contractions were taken to the delivery room after 8 cm. of dilatation. Between contractions pressure was applied to the fetal skull with the examining hand and minimal drops in the fetal heart rate noted. Similar results were obtained when a 3 cm. pessary was placed on the fetal skull and pressure applied.

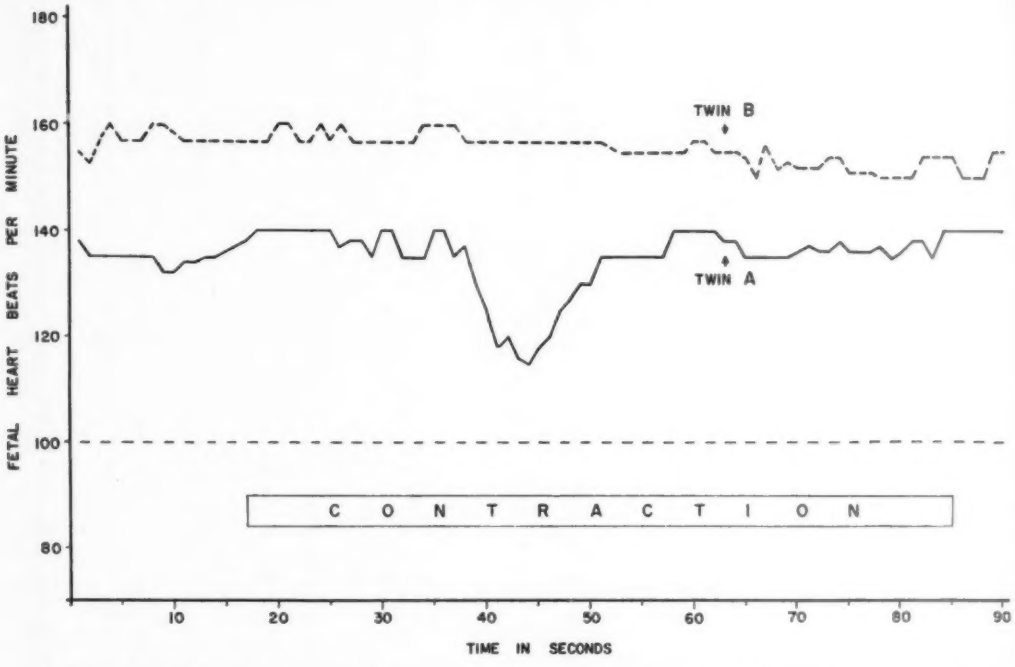


Fig. 7.—Fetal heart rates during a uterine contraction in a twin pregnancy. Twin *A* is in vertex presentation and dilating the cervix. Twin *B* is also in vertex presentation but the vertex is out of the pelvis.

However, when a 6 cm. pessary was applied and pressure exerted, a marked bradycardia similar to that noted with uterine contractions in other labors was obtained consistently. With the apparatus employed, pressures of about 30 to 40 mm. Hg produced this bradycardia. It is difficult to measure accurately the pressure being applied to the fetal skull by a primigravid cervix at the height of a contraction, but since it is well known that intra-amniotic fluid pressures of 50 to 60 mm. Hg are not uncommon with contractions, it seems reasonable to assume that physiologic cervical pressures may be of the same order of magnitude as those experimentally applied via a pessary to the fetal skull. Fig. 6 demonstrates the findings in 2 experimental instances.

To elucidate further the role of the cervix in the production of fetal bradycardia, a primigravid patient who had a twin pregnancy was studied. One twin was presenting by the vertex and was responsible for the cervical dilatation. The other was also presenting by the vertex but the head was out of the pelvis. Both amniotic sacs were intact. Since both placentas were

probably subject to the same intra-amniotic fluid pressures and therefore to similar compression of the placenta, similar bradycardia should have been noted in both fetuses if this is the mechanism of bradycardia. If intracranial pressure due to pressure of the cervix was a significant factor it should have been manifested by fetal bradycardia only in the twin that was dilating the cervix. Careful study of the fetal heart rates of these twins showed that the twin whose vertex was dilating the cervix consistently had bradycardia with contractions while the other twin's heart rate remained relatively constant. Fig. 7 is a graph through one such contraction.

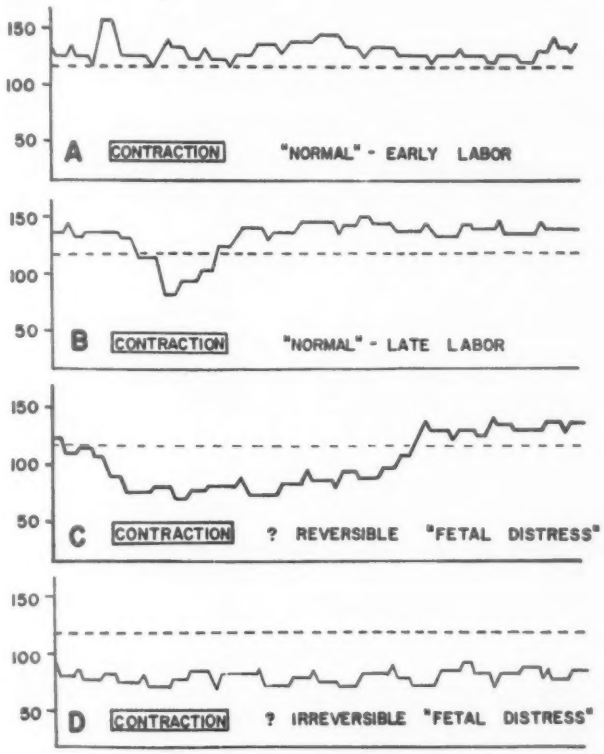
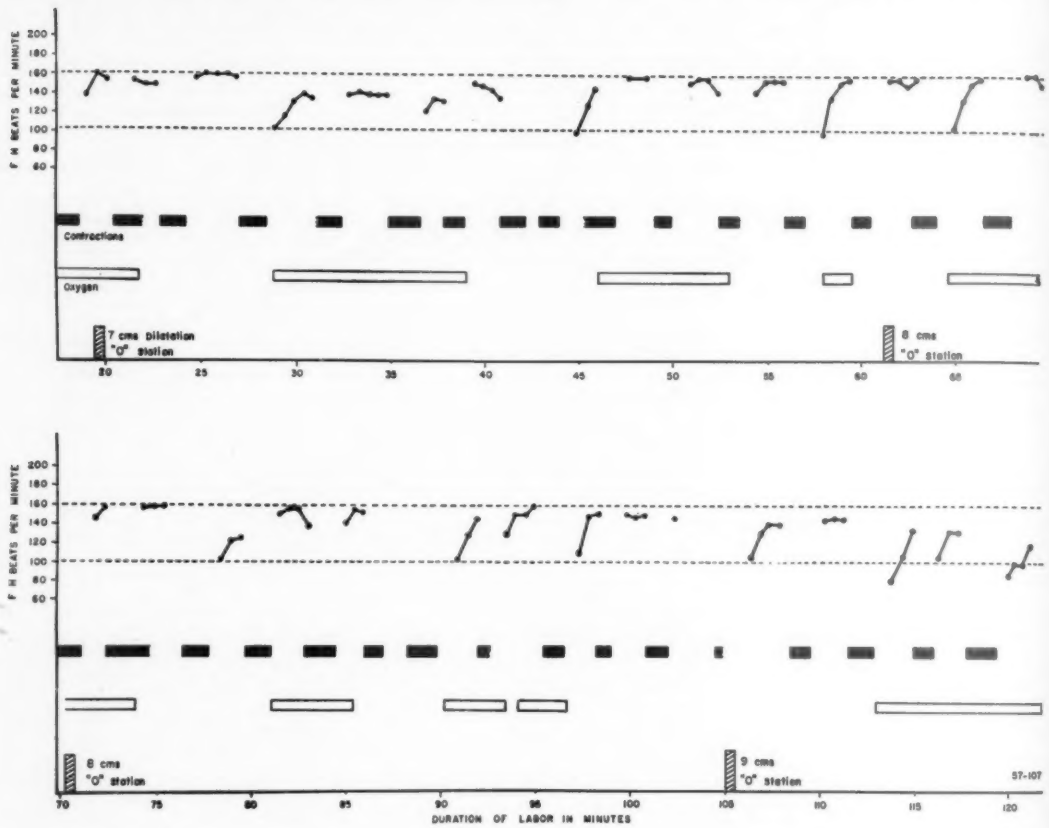


Fig. 8.—A working hypothesis illustrating the possible relationship of fetal bradycardia and fetal distress. The two upper (*A*, before 4 cm. dilatation; *B*, 4 to 8 cm. dilatation) and lowermost (*D*) graphs illustrate our present knowledge of the relationship between fetal heart rates and fetal distress. Both upper graphs are considered to be normal findings and the lowermost graph is usually indicative of severe fetal damage or death. It is postulated that somewhere between the physiologic bradycardia due to contractions and the bradycardia which is persistently less than 100 beats per minute is a period where the fetal heart rate drops lower, and stays down longer than it normally should. This is considered to be the period of "reversible" fetal distress where early intervention may prevent serious fetal damage (*C*).

This probable role of intracranial pressure in fetal bradycardia is also supported by the observation that with contractions bradycardia has not been noted in breech presentations. In this case the fetal skull is being compressed by the smooth uterine fundus.

From available data it seems reasonable to attribute the "physiologic" drop in fetal heart rate at the height of a contraction to an increase in intracranial pressure. The final mechanism by which this is accomplished is not known, but it may be related to variation in blood flow to the brain stem as a result of altered intracranial dynamics.

Working Clinical Hypothesis.—A consideration of the observed clinical and experimental data suggests the possibility of a working clinical hypothesis. It is therefore postulated that there is a transitional area somewhere between the "physiologic" momentary fetal bradycardia which may be as low as 60 to 70 beats per minute at the height of a contraction and the "pathologic" bradycardia that is below 100 beats per minute throughout the interval between contractions.



PRIMIGRAVIDA IN LATE LABOR

Fig. 9.—The average fetal heart rate in late labor. This graph illustrates the average fetal heart rate over a 30 second period as determined in the interval between contractions (omitting the first 30 seconds immediately after the contraction). This is the usually accepted method of determining the fetal heart rate by auscultation. It is interesting to note the relatively short periods of time the fetal heart can be heard in late labor. In only two instances it could have been heard momentarily below 100 beats per minute. Clinically the fetal heart rate was judged to be normal. (Fig. 10 compares this average rate with the instantaneous rate.)

This transitional area is characterized by an accentuation of the "physiologic" bradycardia so that, with a contraction, fetal bradycardia begins earlier, is more profound, and persists beyond the end of a contraction. Such a finding might be consonant with "reversible" fetal distress as contrasted to the later finding where bradycardia is persistent between contractions and is frequently associated with fetal death and therefore may be considered "irreversible."

On the basis of experimental work to date a working clinical hypothesis may be summarized as follows:

1. The instantaneous fetal heart rate determined throughout contractions provides more accurate information than the average rate determined in the interval between contractions.

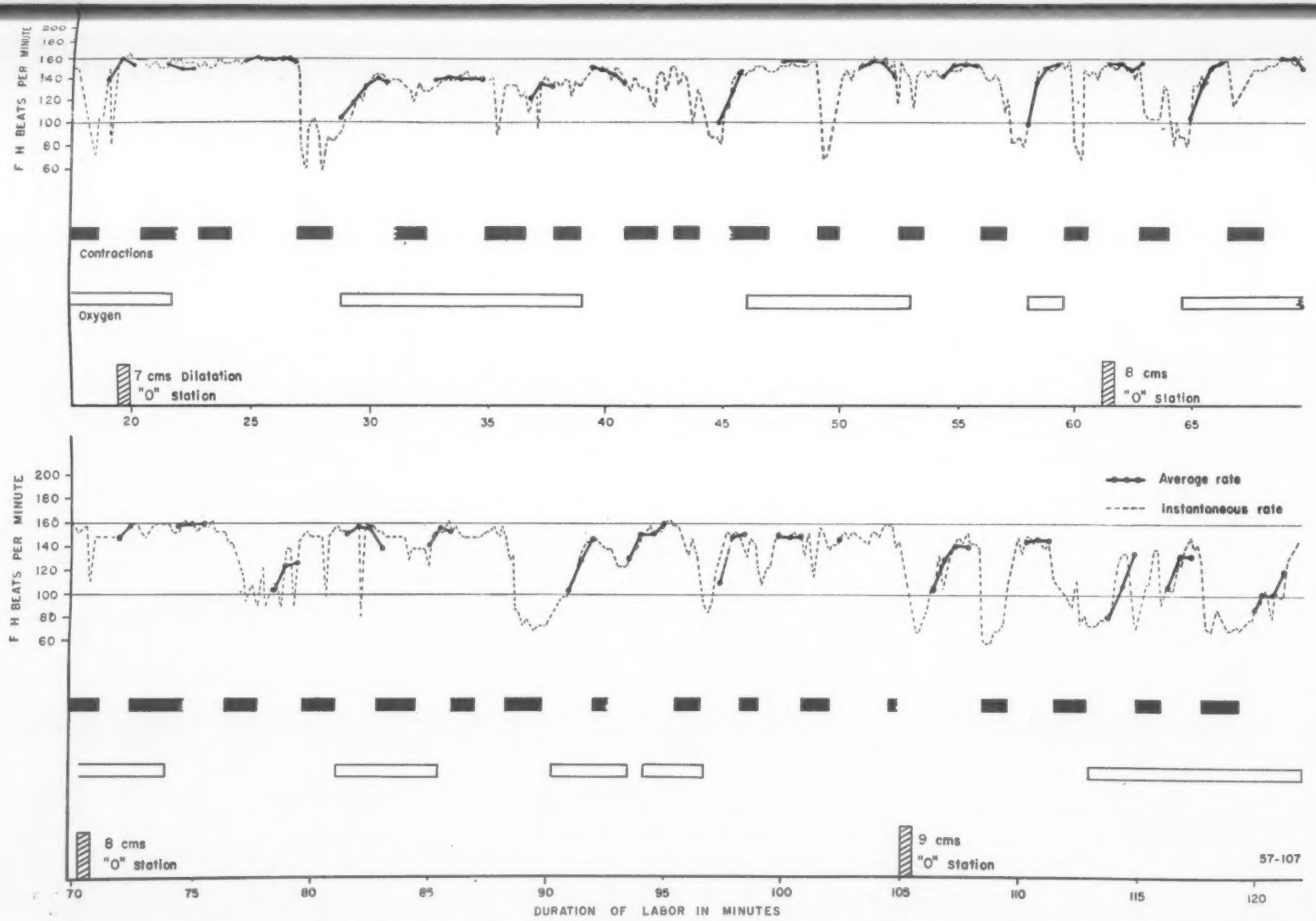
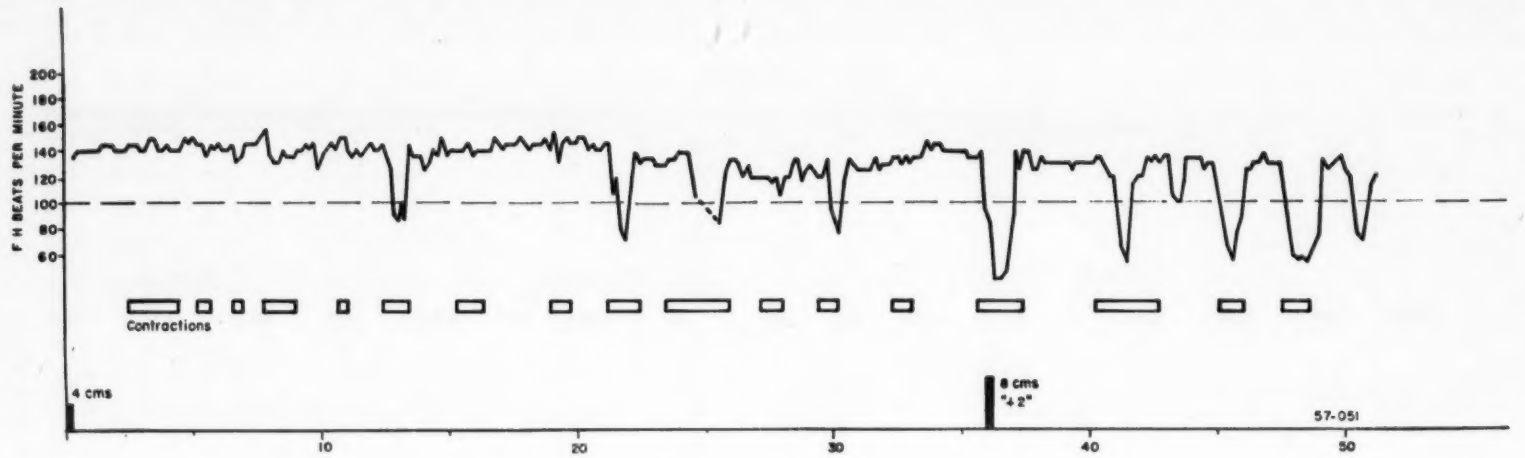
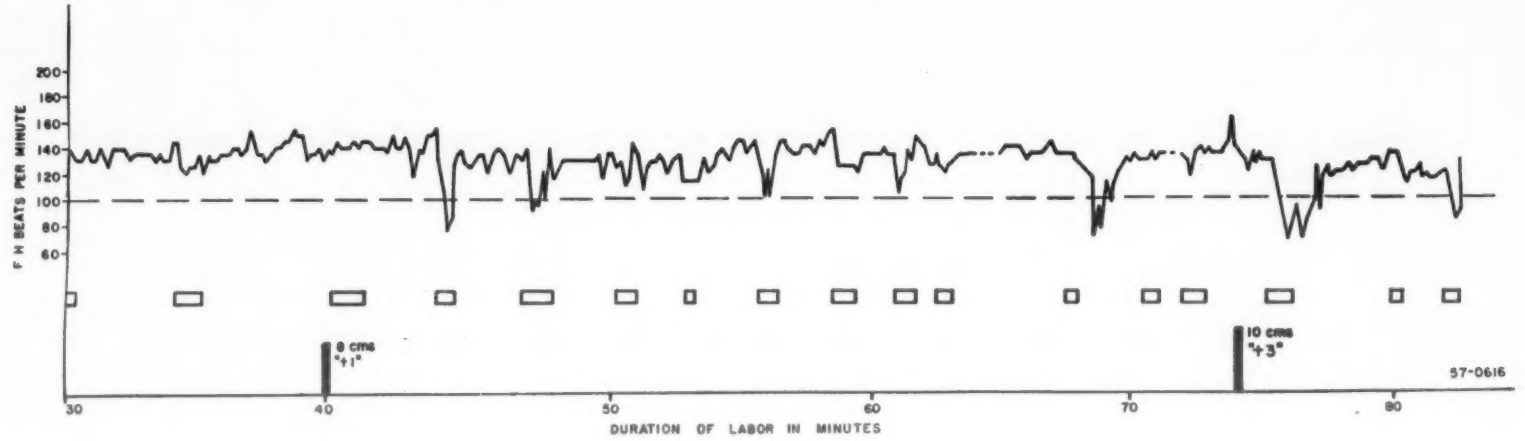


Fig. 10.—A comparison of the average and instantaneous heart rates in late labor. This graph demonstrates the added information provided by the instantaneous fetal heart rate. It can be seen readily that fetal bradycardia is present with contractions and persists for a period when they are over. This finding approximates the situation of "reversible" fetal distress discussed under Fig. 8, *C*. Cesarean section was done for fetal distress. At the time of delivery the umbilical cord was wound tightly around the body and neck of the infant who was flaccid and cyanotic. A mild paresis of the right arm was present for 2 days. This case suggests that the instantaneous fetal heart rate may reveal fetal distress when the average rate is still considered within normal limits.



BREECH PRESENTATION WITH PROLAPSE OF CORD



VERTEX PRESENTATION WITH CORD TIGHTLY WOUND AROUND NECK

Fig. 11.—The probable significance of fetal bradycardia in umbilical cord accidents. In both the above labors no fetal bradycardia had been noted with earlier uterine contractions. Since in the patient with a vertex presentation the cervix was more than 8 cm. dilated and the other patient had a breech presentation, no bradycardia was anticipated. When it was noted, some fetal difficulty was suspected. Subsequent delivery demonstrated the above cord accidents.

2. Fetal bradycardia of 60 to 70 beats per minute during uterine contractions when the cervix is between 4 and 8 cm. dilated is normal in vertex presentations.

3. Fetal bradycardia with contractions at less than 4 cm. or more than 8 cm. of cervical dilatation in vertex presentations or in breech presentations is abnormal and indicates fetal embarrassment.

4. Fetal bradycardia of less than 100 beats per minute throughout the interval between contractions is a relatively late manifestation of fetal distress and intervention at this time is frequently too late since the fetus has been irreversibly damaged.

5. The manifestations of "reversible" fetal distress may be an earlier and more profound as well as persistent fetal bradycardia with contractions, so that the fetal heart rate does not return to normal before the contraction is over.

Fig. 8 is a graph illustrating this hypothesis.

Results

Fig. 9 is the record of a 26-year-old primigravida who was 4 weeks past her due date and in whom, one week prior to labor, the fetal head was not yet engaged. X-ray pelvimetry revealed an adequate inlet. Following admission to the hospital, labor progressed satisfactorily until about 30 minutes before the fetal ECG record was started. On sterile pelvic examination at this time the cervix was 7 cm. dilated with the head at zero station. Light meconium-stained amniotic fluid was noted when the membranes were ruptured. Because of this finding and "postmaturity," the patient was given oxygen. The fetal heart rate was 140 beats per minute and regular. Throughout the remainder of the labor no abnormalities were detected by auscultation.

The fetal heart rate graph of Fig. 9 has been plotted by averaging the rate for 30 seconds in the interval between contractions (omitting the first 30 seconds immediately following a contraction) and would be the data obtained by clinical auscultation. With averaging of the auscultatory findings there are two short periods where the fetal heart rate is momentarily less than 100 beats per minute. The bradycardia was not detected clinically and the graph has been constructed from the data obtained electronically during the course of labor.

The graph of the instantaneous fetal heart rate (Fig. 10) over the same period shows the added information now available. It can be seen readily that even though the cervix is more than 8 cm. dilated, the instantaneous heart rate is dropping with contractions. As labor progresses, bradycardia begins to appear in the interval between contractions. These findings were growing progressively worse in spite of oxygen therapy. A cesarean section performed at this point revealed a flaccid, cyanotic 7 pound, 14 ounce infant who was covered with meconium and did not breathe for about 4 minutes. The placenta was implanted high on the anterior fundus, and the umbilical cord was tightly wound around the infant's body and neck producing some strangulation. After resuscitation the infant appeared to be in good condition except for a mild paresis of the right arm which persisted for 2 days. It seems reasonable to classify this as an instance of fetal distress which did not yet satisfy the present clinical criteria. To date, an additional 4 similar cases have been encountered. It appears therefore that the instantaneous fetal heart rate may provide a more sensitive index of fetal distress than averaging the rate.

Among the more common problems of labor are accidents involving the umbilical cord. Fig. 11 demonstrates fetal heart rates in 2 instances where difficulties were suspected from electronic evaluation many minutes before they were clinically recognized. The upper tracing *(57-051)* shows the late first stage

Fig. 11.—The probable significance of fetal bradycardia in umbilical cord accidents. In both the above labors no fetal bradycardia had been noted with earlier uterine contractions. Since in the patient with a vertex presentation the cervix was more than 8 cm. dilated and the other patient had a breech presentation, no bradycardia was anticipated. When it was noted, some fetal difficulty was suspected. Subsequent delivery demonstrated the above cord accidents.

Fig. 12.—Severe fetal arrhythmia in a term pregnancy. This graph of the instantaneous fetal heart rate demonstrates arrhythmia of a magnitude only occasionally seen. Small vertical lines have been drawn coincidentally with the fetal ECGs so that the pattern is seen more easily. Because of the relatively high average value of this arrhythmia, fetal distress was not thought to be present. The physician in charge of the patient felt that this degree of irregularity was indicative of fetal distress. The cesarean section performed within minutes of taking this record revealed a normal infant in good condition.

of a breech labor where no fetal bradycardia is usually noted with contractions. Approximately 35 minutes before delivery such bradycardia was noted. This recurred with increasing frequency and magnitude. The obstetric staff was notified of possible difficulties and the patient was taken to the delivery room where the umbilical cord was found prolapsed between the thighs in a double footling breech presentation.

The lower tracing *(57-0616)* shows fetal bradycardia with contractions after 8 cm. of dilatation in a case where no previous fetal bradycardia had been noted. Incipient fetal distress was anticipated and at delivery the umbilical cord was tightly wound around the neck of the fetus.

Fig. 12 is an example of extreme fetal cardiac arrhythmia observed in a term pregnancy. The mother was not in labor. Arrhythmia of this magnitude and duration appears infrequently, and is thought to be of no pathologic significance since similar but less pronounced arrhythmias have been noted in "normal" labors. The fact that the average rate here is relatively normal gives added support to this idea. A cesarean section performed for "fetal distress" by the private obstetrician disclosed a normal infant.

Comments

From present data, it appears that the instantaneous rate-time graph of "physiologic" bradycardia has a different configuration from that of the "pathologic." In the latter instance the bradycardia is usually more profound and persistent, so that the graph has steeper sides and a blunter trough which becomes progressively wider until it encroaches on the interval between contractions. Preliminary detailed beat-to-beat studies of the "physiologic" bradycardia suggest that it is frequently preceded and followed by momentary tachycardia whereas the "pathologic" bradycardia is not. Such a fine differentiation will require extensive study before any conclusions can be reached.

Throughout this study we have been concerned only with the fetal heart rate. The use of changes in the fetal ECG configuration as an index of abnormal fetal environment has been reported previously.[15] In our experience, the uncertain position of the electrodes and the varying configuration of the fetal ECG during the course of labor have rendered this of little value. In addition the fetal P and T wave potentials are usually too small to be seen above the extraneous electrical and skin noise levels encountered in the average labor room. In cases where unquestioned fetal distress was noted, the changes in the fetal heart rate were quite apparent, whereas consistent fetal ECG configuration changes could not be detected.

Present studies of fetal ECG configuration in a screened area relatively free from electrical interference and the use of especially constructed low-noise preamplifiers may provide further knowledge concerning the possible association of fetal P and T wave changes with fetal anoxia.

In the near future multichannel electronic apparatus will be used to record simultaneously on magnetic tapes the fetal heart rate, intra-amniotic fluid pressure, and cervical pressures. This storage method will provide data which can be processed later in detail with an extensive semiautomatic data reduction system. In this way a statistically significant number of patients may be studied in a reasonable time.

Summary

1. Modern electronic techniques provide a more accurate indication of the fetal heart rate during normal and abnormal labor than it is possible to obtain by present clinical methods.

2. With normal breech presentations and the majority of vertex presentations studied, the fetal heart rate does not slow significantly with contractions.

3. In the minority of vertex presentations, usually in primigravidas, the instantaneous fetal heart rate may drop as low as 60 to 70 beats per minute and may return to normal 10 to 15 seconds before the contraction is over.

4. In vertex presentations, fetal bradycardia with contractions is probably related to an increase in intracranial pressure which in turn is related to the amount of cervical dilatation present.

5. A preliminary evaluation of a working clinical hypothesis based on changes in the instantaneous fetal heart rate suggests the possibility of a more sensitive index of fetal distress.

Conclusion

The use of modern electronic techniques for the evaluation of changes in the fetal heart rate during labor and delivery may permit a more valuable and accurate identification of fetal distress than is at present available by clinical methods.

I wish to thank Dr. O. W. Hess, Dr. Frank Chung, and the research nurses who have played an important part in the collection and processing of data for this preliminary report.

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FETAL RESPIRATION DURING THE SECOND STAGE OF LABOR IN RABBITS AND THE ORIGIN OF PULMONARY HYALINE MEMBRANE*

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IN THE present investigation, the aim is to determine the changes which occur in the contents of the air passages of the lungs of rabbit fetuses during labor. Evidence that fetuses breathe the fluid in which they are immersed during labor is closely linked with clarification of the cause of pulmonary hyaline membrane disease. In view of the evidence that breathing is a normal part of fetal life and that intrauterine respiratory movements result in a tidal flow of amniotic fluid into the lungs,[1] it is of immediate interest to demonstrate to what extent the breathing of fluid by the fetus occurs during passage through the birth canal in the second stage of labor.

In the environment of the fetus in the birth canal, the presence of foreign matter such as blood, cellular debris, and mucoid fluid commonly found during labor provides tracer material which may be readily identified after entrance into the fetal air passages. Even though the fetus succumbs in the course of expulsion or dies within a few hours following delivery, evidence of fetal respiration during labor is afforded by the contamination of the airways with blood and cellular debris which surround the fetus for a variable period of time.

In the current descriptions of injuries of the respiratory organs which are associated with a fatal outcome of labor, what has often been overlooked is the physiological factor—the breathing of fluid by the fetus before birth. For instance, at present much interest has centered upon hyaline matter in the lungs of newborn infants, which may be distributed over extensive areas of the alveoli and bronchioles like a membranous lining. Uncertainty as to the nature and origin of this eosinophilic hyaline matter is such that numerous recent investigators have rejected a source outside of the lungs and have attributed it primarily to injury of the pulmonary tissues. The hyaline formation has been ascribed to a variety of causes such as disturbances of the pulmonary circulation,[2, 3] degenerative lesions of the air passages,[4, 5, 6] and toxic changes.[7, 8] Evidence that fetuses breathe the fluid which surrounds them during labor is closely related to establishment of the nature of hyaline membrane disease.

The changes which are found in the lungs at autopsy in babies who die as a result of labor have been set forth in numerous investigations and were reviewed[9, 10] with special reference to the findings in intrauterine pneumonia,

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atelectasis, and asphyxia. The comprehensive survey[9] in 1949 of previous autopsy results was undertaken in an effort to correlate the changes in the lungs with fresh evidence of the importance of fetal respiratory activity before birth and to point out the consequences of breathing contaminated amniotic fluid. Further reports in recent series of autopsies from many localities make clear the great frequency with which obstruction and structural abnormalities of the air passages are associated with perinatal death.[10-17] Uncertainty, however, is often expressed regarding the role of fetal respiratory movements as an active factor which causes entrance of foreign matter into the lungs and leads to obstruction.

In order to obtain fresh evidence of the relation of the physiological activity of the fetal respiratory organs during labor to the pathological changes found in the lungs at autopsy, the problem has been carried over to a laboratory animal, the rabbit, in the present investigation. The lungs of rabbit fetuses, stillborn or dead in the early neonatal period as a result of labor, have been examined routinely at autopsy, just as has been done in the human. Under conditions of laboratory control in the rabbit, in which fetal respiratory activity has been studied in more detail than has been possible in the child, new evidence is obtained concerning the role of fetal respiration in the origin of obstruction and abnormalities of the air passages.

Method and Material

The present observations are based upon autopsies of 117 rabbits born at full term, of which 76 were stillborn and 41 were alive at birth but died within 24 hours. The autopsies were obtained from 55 litters in which at least one death occurred during labor or shortly afterward; the total births were 241, among which 147 fetal or neonatal deaths occurred; of these, 117 were autopsied, and the lungs were examined microscopically.

In addition to the series of fetal and neonatal deaths, observations have also been made upon a control group of 164 newborn rabbits that were sacrificed within 12 hours after birth following labor in which the outcome was not complicated by any deaths. These were the total number born in 30 consecutive litters. The lungs of these newborn rabbits were obtained at autopsy. All were at full term, 31 or 32 days, and showed normal activity. For sacrifice, chloroform inhalation was used.

Formalin (10 per cent) was used for fixation, and sections of the lungs about 8 μ in thickness were stained with hematoxylin and eosin for microscopic examination. An especially favorable opportunity to determine any changes in the contents of the air passages of the lungs during labor is offered by the circumstance that in newborn rabbits a view of all lobes of both lungs is readily obtained in a single longitudinal section. Microscopic examination of the alveoli and bronchioles for evidence of foreign matter such as cells and debris found in the birth canal during labor may thus be more complete and accurate in rabbits that die during the second stage of labor or soon afterward than is the case in the lungs of human fetuses under similar circumstances.

Observations

A. Stillbirths and Neonatal Deaths.—On removal at autopsy the lungs of stillborn fetuses were uniformly dark red and sank in formalin. In contrast,

the lungs of animals that died following birth floated in formalin. The external appearance varied because of pale pink areas which ranged in extent from complete involvement of the entire lung to irregularly scattered patches of widely different size and pattern.

The outstanding result of microscopic examination of the lungs of stillborn rabbits and of those that died soon after birth is the evidence that the fluid and cellular contents of the birth canal entered the alveoli and larger air passages of the lungs in more than 90 per cent of the 117 animals autopsied. Erythrocytes and a variety of cells and debris were scattered throughout the lungs in 72 of the 76 stillborn fetuses, and in 37 of the 41 that died in the early neonatal period, or 94 per cent and 90 per cent, respectively. The extensive dispersal of red blood cells usually in masses along the bronchioles and in the alveoli in 109 of the 117 lungs of the series was strikingly revealed by the hematoxylin and eosin stain. In addition there were epithelial cells and amorphous debris like that found in the birth canal during labor, all of which may be intermingled throughout the lungs.

Quantitative determination of the amount of foreign matter seen in longitudinal section of all lobes of both lungs showed that large areas of both lungs contained blood, cells, and amorphous debris in 32 of 76 stillborn fetuses, and in 17 of 41 newborn which died within a few hours, or 42 per cent and 41 per cent, respectively. In this group extremely dense concentrations of blood and debris were found obstructing most of the alveoli and bronchioles throughout both lungs in 9 of the stillborn fetuses, or 12 per cent of 76, and in 6 that died neonatally, or 14 per cent of 41. Small amounts of blood and debris were evident in the air passages of the lungs of 40 fetuses and of 20 newborn which died, or 53 per cent and 49 per cent, respectively. No blood was noted in the alveoli and bronchioles of the lungs of 4 stillborn and 4 newborn which died, or 5 per cent and 10 per cent, respectively.

Photographs of microscopic sections of the lungs showing foreign matter of the birth canal in the air passages of fetuses that died during labor or soon afterward have been obtained from 7 litters. The contents of the alveoli and bronchioles as found in stillborn fetuses are illustrated in Figs. 1 to 6; and in Figs. 7 to 10 are shown the changes following the breathing of air by newborn rabbits that died within a few hours.

The lungs in Figs. 1 to 6 were obtained from 5 fetuses born dead at term in 5 different litters. In all cases the lungs sank upon immersion in formalin solution after removal at autopsy and showed a uniformly dark red appearance typical of airless lungs. In Fig. 1, in a section obtained from the lung of a stillborn fetus expelled at 32 days, it is evident that, instead of the amniotic fluid which normally fills the air passages before the onset of labor, there is massive contamination of the alveoli and bronchioles as shown by the entrance of large numbers of red blood cells. Nucleated cells and amorphous debris are intermingled with the blood in the air spaces, and the foreign matter is widely scattered throughout the lungs.

In Fig. 2, in a large bronchiole of the same lung, epithelial cells and amorphous debris in large amount are mixed with erythrocytes. The foreign matter in the lungs appears identical with that commonly found in the birth canal during labor.

In Fig. 3, in a large bronchiole of a fetus expelled in a different litter at 32 days, considerable amorphous debris is evident along with nucleated cells and erythrocytes. The foreign matter in the fetal lungs appears similar in the chief histological elements but varies with respect to the relative proportion of the components.

In Fig. 4, in a section obtained from a fetus expelled at 32 days, clumps of erythrocytes are scattered throughout the alveoli. Epithelial cells, a few leukocytes, and amorphous debris are also evident in alveoli and in an adjacent bronchiole.

In Fig. 5, in a section obtained from a stillborn fetus at 32 days, a massive concentration of red blood cells, epithelial cells, and amorphous matter occupies the alveoli and bronchioles. A similar dense concentration of foreign matter is found throughout the air passages of both lungs.

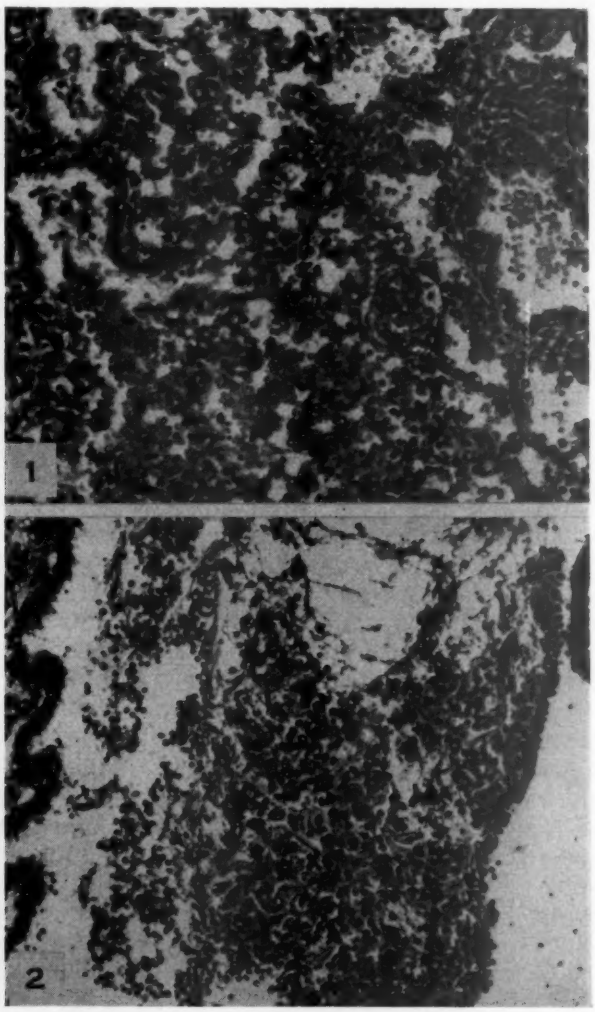

Fig. 1.—Lung of stillborn rabbit; massive contamination of alveoli. (×275; reduced ⅓.)
Fig. 2.—Same section as Fig. 1; cellular debris of birth canal in large bronchiole. (×275; reduced ⅓.)

In Fig. 6, in a section from the lung of a fetus expelled at 33 days, erythrocytes and debris are present in bronchioles and alveoli near the pleural surface. The central as well as peripheral areas of both lungs show similar accumulations of foreign matter.

Of special interest is the foreign matter in the lungs of fetuses which survive passage through the birth canal but succumb within 24 hours following birth. In Fig. 7, in a section obtained from the lung of a newborn rabbit which

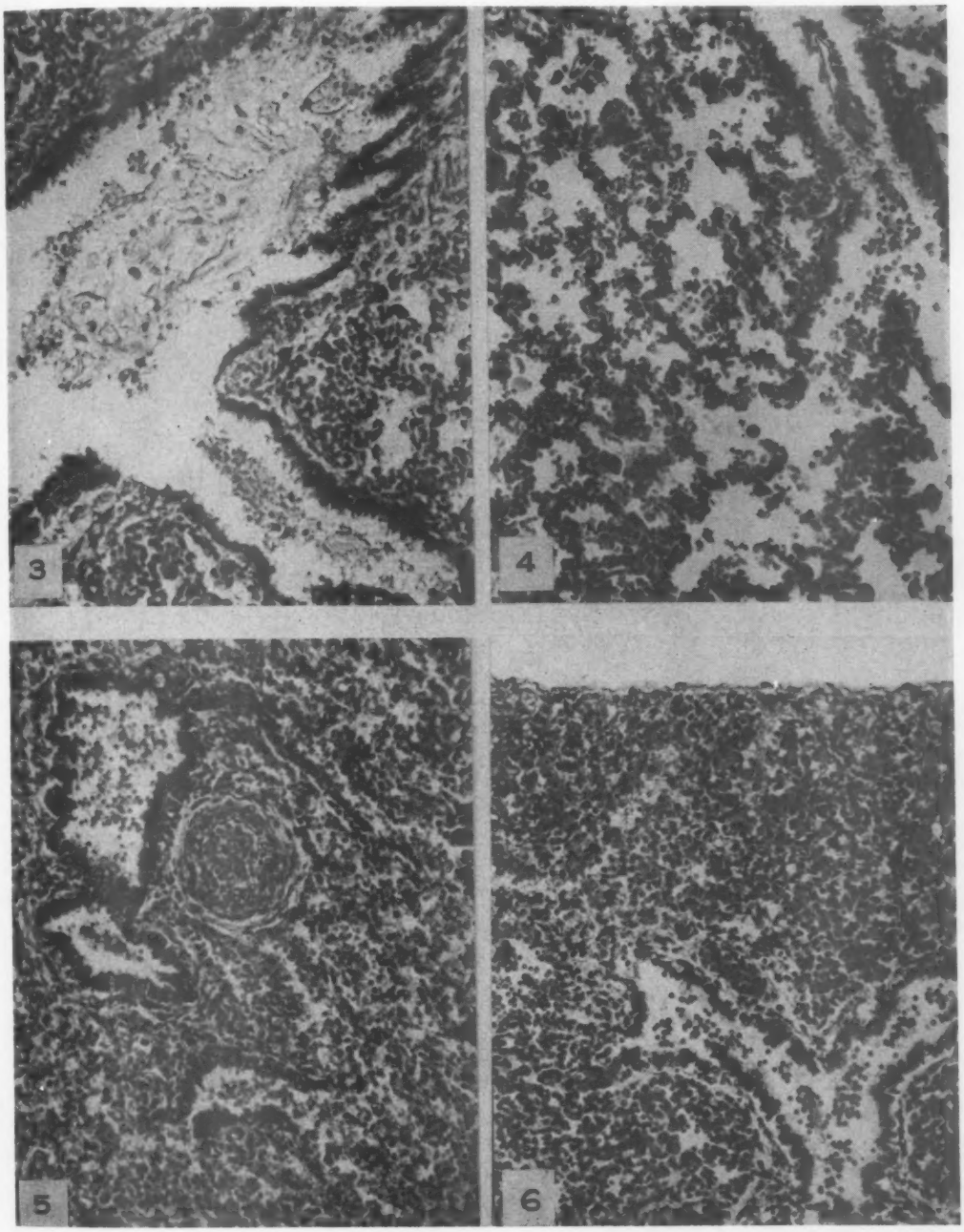

Fig. 3.—Bronchiole of stillborn rabbit; epithelial cells, blood, amorphous debris. (×275; reduced ⅓.)

Fig. 4.—Stillborn rabbit; foreign matter scattered in bronchioles and alveoli. (×275; reduced ⅓.)

Fig. 5.—Stillborn rabbit; blood and cellular debris obstruct air passages. (×275; reduced ⅓.)

Fig. 6.—Stillborn rabbit; blood and debris near pleural surface. (×275; reduced ⅓.)

died within several hours after birth at term, 32 days, there are dense accumulations of foreign matter, especially red blood cells. The lungs floated upon immersion in formalin, and the uniform dark red color characteristic of airless lungs was interspersed with bright pink areas scattered widely in irregular pattern. Microscopically, dilated alveoli such as mark the entrance of air into

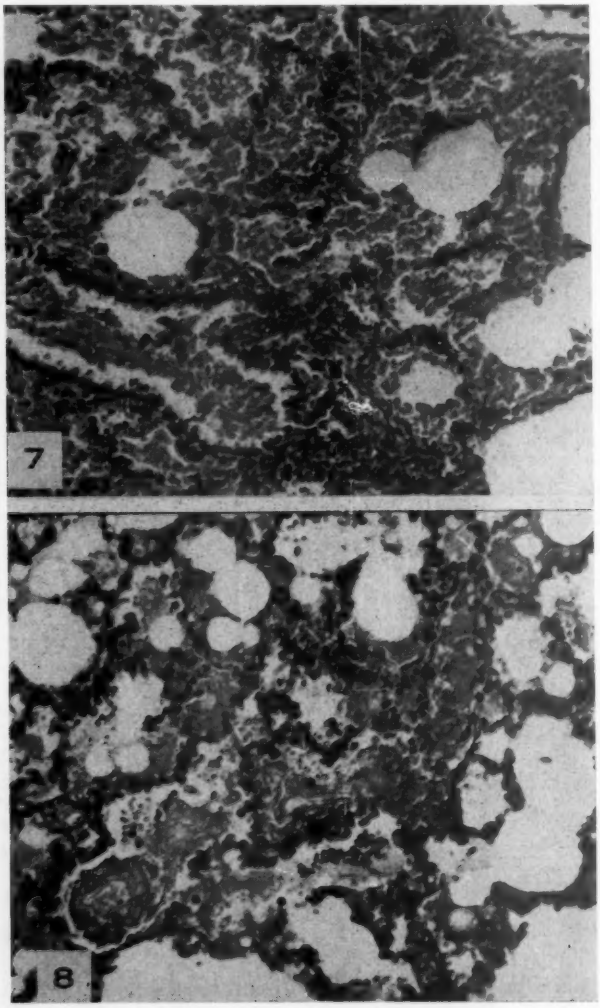

Fig. 7.—Newborn, died within few hours; entrance of air and displacement of alveolar contents in a layer or film along the walls. (×275; reduced ⅓.)

Fig. 8.—Newborn, died within few hours; membranelike dispersion of alveolar contents following entrance of air. (×275; reduced ⅓.)

the lungs are evident, as well as less expanded alveoli which remain completely occluded by erythrocytes and debris. In the air passages which are not completely obstructed, the entrance of air and expansion of the air spaces results in distribution of the contents of the air passages along the walls in a film or layer.

In Fig. 8, in a section obtained from the lungs of a full-term rabbit which died within a few hours after birth at 33 days, a dense concentration of amorphous debris staining with eosin and mixed with erythrocytes and nucleated cells occludes many alveoli completely or in part. In the terminal air spaces which

are not completely obstructed, as shown by the dilatation which occurs with the entrance of air, the foreign matter outlines the walls of the air spaces like a lining membrane. In numerous alveoli and bronchioles which remain completely occluded by foreign matter, the air spaces are not collapsed but remain in the state of partial expansion that is characteristic of intrauterine existence

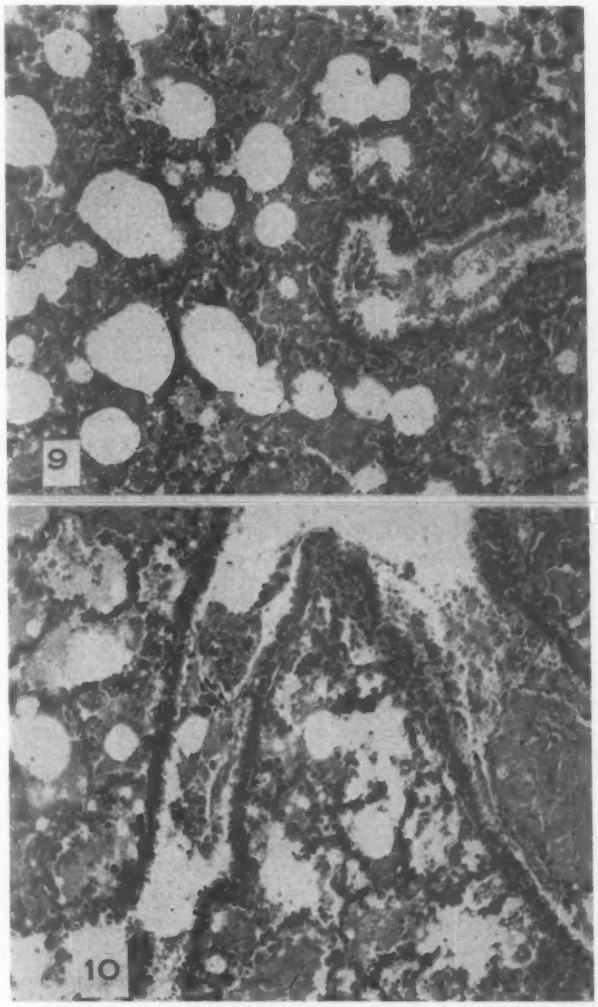

Fig. 9.—Same section as Fig. 8: massive contamination of alveoli; some filled with foreign matter; others dilated and contents distributed like a membranous lining. (×230; reduced ⅓.)

Fig. 10.—Bronchioles in same section as Fig. 8, containing epithelial cells, blood, and amorphous debris of the birth canal. (×230; reduced ⅓.)

before the onset of the breathing of air. The lungs floated upon immersion in formalin, and extensive bright pink areas were scattered widely among the dark red regions.

In Fig. 9, in the same lung, the entrance of air in numerous alveoli is marked by displacement of the eosinophilic cellular and amorphous debris in a membranelike layer along the walls of the expanded air passages. Other alveoli remain occluded by the foreign matter and in a state of expansion similar to that of stillborn fetuses.

In Fig. 10, in a large bronchiole of the same lung, the mixture of amorphous matter, epithelial cells, and blood is like that which surrounds the fetus in the birth canal. In a few alveoli the entrance of air is not completely obstructed.

In addition to the membranelike distribution of the foreign matter in areas of the lung in which the entrance of air is not totally occluded, emphysema and regions of atelectasis are evident like those which follow obstruction. The state of dilatation of the alveoli, which is characteristic of normal fetuses before the onset of the breathing of air, is commonly noted in alveoli which remain completely filled with cellular debris and red blood cells. Decrease in expansion of the alveoli or collapse like that following resorption of the air or fluid contents is also found adjacent to bronchioles and alveoli which are completely obstructed with foreign matter.

B. Normal Newborn.—The significance of the striking alteration of the contents of the air passages of fetuses that died during labor or soon afterward is further revealed by the findings in the lungs of the control series of newborn rabbits which were sacrificed within a few hours after birth following uncomplicated labor. In the microscopic examination of the lungs of 164 newborn rabbits obtained from 30 litters sacrificed by chloroform inhalation, there was no case in which massive accumulation of blood, epithelial cells, and amorphous debris intermingled throughout large areas of both lungs, such as characterized the microscopic picture in about 40 per cent of the lungs of the stillborn rabbits and those that died neonatally. Only minor quantities of erythrocytes and cellular debris were scattered in the air passages. In two lungs a few alveoli in several small areas were obstructed by red blood cells and debris. In about half of the lungs erythrocytes were sparsely distributed in small clusters in alveoli and bronchioles of widely scattered areas. In the remaining half of the series, erythrocytes were few, being found frequently along the wall of the air spaces with other nucleated cells and debris, and might have escaped notice easily if sections had failed to include all lobes of both lungs. Various nucleated cells like those present in the birth canal were evident especially along the surface of the bronchioles, including the larger ones. In the lungs of 65 animals the cells and debris accumulated in sufficient amount to outline clearly the walls of many bronchioles. There was no evidence of obstruction to the entrance of air into the bronchioles and alveoli by the relatively small amounts of cellular debris.

C. Abnormal Labor.—The frequency and magnitude of the contamination of the air passages of the fetus with foreign matter of the birth canal reveal the fetal respiratory organs to be in a state of functional activity during labor. In an environment of fluid containing blood, bacteria, and cellular debris, the fetus breathes. Under these circumstances, impairment of the labor mechanism, which prolongs exposure of the fetus to unfavorable surroundings before birth, is of outstanding significance with consequences that extend far beyond the time of birth.

Evidence of abnormality of labor is revealed by (1) prolonged duration and by (2) lethal outcome for the fetus. Marked prolongation of labor, with fetuses expelled at intervals during the course of many hours instead of within a half hour as normally occurs, was observed in 30 per cent of the 55 litters in the series; of 85 offspring in this group of 17 litters there were 59 deaths, or 69 per cent; 48 of these fetuses were autopsied, 40 stillborn and 8 that died in the neonatal period. In the entire series of 55 litters, fetal and neonatal mortality reached 61 per cent in 241 full-term offspring, or a total of 147 deaths;

in contrast, in the control series of rabbits in the same colony, perinatal mortality averaged less than 6 per cent in more than 1,000 births at term. Evidence of the magnitude of the failure of the labor mechanism to achieve the birth of normal offspring despite full-term development of the fetuses is revealed by the incidence of fatalities in individual litters. Of 117 autopsies obtained from 55 litters, 76 were performed on stillborn fetuses which were distributed in 37 of the 55 litters; and 41 were on liveborn fetuses that died neonatally, involving 22 litters. Of the fetuses autopsied, all were stillborn in 9 litters of 37 fetuses, and all died neonatally in 17 litters in which 27 newborn died; in the remaining 29 litters there were both stillbirths and neonatal deaths, 39 of the former and 14 of the latter.

Comment

In the light of the evidence that the contents of the fetal air passages consistently show changes at the termination of labor which reveal the entrance into the lungs of fluid and foreign matter of the birth canal, it is clear that the fetus breathes during the period of expulsion, the second stage of labor. Change of environment parallels change in the content of the air passages. During the stage of expulsion the fetus does not remain dormant. In fact, the activity of the fetus becomes a leading factor in the pathology of labor. In the course of parturition fetal respiration emerges from the relative obscurity of a physiological function to become a hazard to survival.

A striking illustration of such hazard is pulmonary hyaline membrane disease. The entrance of fluid and cellular debris of the birth canal into the fetal air passages during labor accounts for the origin of foreign matter in the lungs of the newborn; the displacement of the eosinophilic matter in a membranelike layer along the walls of the alveoli and bronchioles results from the expansion of the air passages with the entrance of air. Furthermore, the hazard for the fetus in prolonged labor is not merely deprivation of oxygen; there is also an increase in duration of exposure to a fluid environment containing blood and bacteria. Despite improvement in the oxygen supply following delivery, the consequences of contamination of the air passages during labor extend in many instances far beyond the time of birth.

From an early period of embryonic life the breathing of the fetus in the intrauterine environment is readily demonstrable.[18] In a physiological role fetal respiration promotes a tidal flow of amniotic fluid into the lungs in the course of the normal development of the air passages.[19] With the onset of labor such functional activity leads not infrequently to pathological consequences. At the time of emptying of the uterus the fluid in which the fetus is immersed may undergo extreme alteration within a brief interval. As a result of this change in the fluid environment, the significance of fetal breathing of fluid must be viewed in a new light. Fetal respiration becomes a major factor in exposure of the fetal air passages to contamination and injury immediately following rupture of the membranes. As the fluid which surrounds the fetus changes in content from the time of rupture of the membranes until the onset of the breathing of air, there arises the risk that any fetal respiratory movements may result in the breathing of contaminated fluid containing foreign matter found in the birth canal such as bacteria, blood, mucus, and cellular debris. How great the hazards of fetal breathing actually prove to be during the emptying of the uterus is demonstrated by the high incidence of the entrance of foreign matter of the birth canal into the lungs and the magnitude of the contamination of the air passages, as seen in the present series of autopsies.

Change in the contents of the air passages parallels change of environment whether this occurs before labor, during labor, or after birth. The functional

significance before birth of the integrated movements of the fetal chest and diaphragm, the respiratory excursions, has generally been overlooked despite their indispensable role from the moment of birth. That the breathing of amniotic fluid is a normal function of fetal respiration first became clearly demonstrable *ad oculos* when an experimental method was developed which permitted direct observation of rabbit fetuses showing rhythmic respiratory movements within the unopened uterus. In breathing fetuses amniotic fluid stained with carbon particles reaches the pulmonary alveoli in less than a minute, while in apneic littermates the contaminated amniotic fluid fails to enter the lungs. A tidal flow of fluid occurs with breathing before birth, just as a tidal flow of air occurs with breathing after birth.[20]

A cardinal feature of normal labor is expulsion of the fetus in a state of normal activity including that of respiration. From this standpoint, injury of the newborn, as shown by the presence of respiratory depression, is a sensitive indicator of abnormality of the labor mechanism. Whatever the cause of delay in birth until asphyxia occurs, a factor to be reckoned with in the final outcome of parturition is the breathing of the fetus itself during the second stage of labor. Prolongation of labor is a striking feature in the present series in which fetuses died. Especially noteworthy is the fact that the consequences of impairment of the labor mechanism extend far beyond the mere deprivation of the fetus of oxygen; by prolongation of the exposure of the fetus to a fluid environment which contains harmful foreign matter and bacteria, there results contamination of the air passages, and the fate of the fetus is influenced long after the termination of labor.

Asphyxia neonatorum has long been recognized as the leading cause of fetal death and as a major factor in neonatal mortality. In so far as respiratory failure at birth, whether complete or partial, is linked with impairment of the labor mechanism, it is evident from examination of the lungs at autopsy that not only is oxygen want present but in most cases of fatal outcome there is also contamination of the air passages with foreign matter of the birth canal. Paradoxically, the occurrence of fetal apnea at birth provides a clue to the occurrence of fetal breathing in the birth canal.

In the present series of autopsies the contents of the birth canal are readily identified in the air passages of the vast majority of stillborn fetuses as well as in the lungs of the newborn that died within 24 hours. In the lungs of animals which have breathed air in contrast to the lungs of stillborn fetuses, however, a striking change in the dispersion of the foreign matter along the walls of the air spaces is at once evident. The expansion of the alveoli with the entrance of air is marked by displacement of the foreign matter in a film or layer which outlines the alveolar walls and bronchioles. The air spaces appear to have a lining membrane. The membranous layer stains with eosin and is readily distinguished from the alveolar walls and the epithelium of the bronchioles. The various constituents of the contents of the birth canal which enter the lungs, such as erythrocytes, cellular and amorphous debris, are readily identified in the membranous lining of the expanded air spaces, although mingled in proportions which vary widely. At one extreme, amorphous matter is predominant and lies along the alveolar walls and the bronchioles in a layer that appears homogeneous like a hyaline membrane. At the opposite extreme, erythrocytes or various nucleated cells are so densely distributed that amorphous matter is obscured. Similarly, in the air spaces which contain foreign matter but which remain completely obstructed to the entrance of air, the amorphous and cellular components are intermingled in various proportions. The amount of amorphous matter is more difficult to determine than is the relative concentration of erythrocytes and nucleated cells.

The striking picture of air spaces outlined by a layer of foreign matter following the expansion of the alveoli with the entrance of air, and the absence of such membranelike dispersion of the alveolar contents in airless lungs of stillborn fetuses are demonstrated under especially favorable circumstances in rabbits. The contents of the same birth canal gain entrance to the lungs of fetuses of a single litter in which the outcome of labor results in stillborn fetuses as well as in neonatal deaths. In littermates, whether stillborn or those that die within a few hours after birth, there is a striking similarity in the histological components of the foreign matter in the air passages. Distribution of the contents of the alveoli and bronchioles in a membranelike layer is found after the entrance of air; however, in stillborn littermates, although identical foreign matter is present in the lungs, displacement of it in the form of a film has not occurred. Thus, in the course of parturition of the type that is characterized by multiple births. the influence of dilatation of the air passages with the entrance of air upon the distribution and fate of the alveolar contents stands out with exceptional detail.

The identification of the same type of cells and amorphous debris in the air passages of the fetuses that die neonatally as is present in stillborn littermates is facilitated by the structural development of the lungs which is found in animals at full term, and by the decreased susceptibility of the mature fetus to certain pulmonary changes that are commonly associated with prematurity. Even in the presence of massive contamination of the air passages such as was noted in 12 per cent of the stillborn and in 14 per cent of those that died in the neonatal period, the state of dilatation of the alveoli at term is such that the histological characteristics of their contents are clearly evident, and readily distinguished from the surrounding lung tissue. The presence of atelectasis or incomplete dilatation of the alveoli in areas of the lungs marked by membranelike dispersion of the foreign matter is easily understood as a further manifestation of obstruction of the air passages. Resorption atelectasis involving the obliteration of alveolar spaces that contain little or no foreign matter is a subordinate part of the histological picture in lungs of the present series of full-term rabbits which died within 24 hours.

On the other hand, in numerous series of autopsies of premature babies who have survived for hours or days following birth, extensive areas of collapsed alveoli or resorption atelectasis have been noted consistently, especially in the early stages of prematurity. In the air passages in which the entrance of air was not completely obstructed, especially in the bronchioles, membranelike deposits of eosinophilic hyaline matter have been observed in about 40 per cent of autopsies of premature infants.[16] In view of the increased susceptibility to pulmonary changes such as atelectasis at early stages of viability, even in the absence of hyaline matter, it is not difficult to understand the development of obstruction of extreme proportions in prematures when the additional factor of the entrance into the air passage of foreign matter of the birth canal is superimposed.

When the fatal outcome of labor is viewed in the light of the microscopic examination of the lungs in the present series of 117 autopsies of rabbits at term, the significance for the fetus of impairment of the labor mechanism comes into clear view. In the 76 fetuses that died during labor and the 41 in which death occurred a short time after birth, it was evident upon microscopic examination that the contents of the birth canal were present in large areas of both lungs in 40 per cent of each, the foreign matter being extremely dense in one third of each, or 13 per cent. In the remaining 60 per cent of the autopsies, a fatal outcome of labor was associated with relatively minor contamination of the air passages. Thus, in addition to contamination of the air passages during labor,

there is evidence of fetal injury at the functional level, such as asphyxia, in which little structural alteration is found. In magnitude, however, functional injury of the fetus ranks as a leading cause of death.

Summary

1. Evidence of fetal respiration in rabbits during the period of expulsion, the second stage of labor, is the entrance of the fluid and cells of the birth canal into the air passages.

2. After labor complicated by perinatal deaths, the lungs or more than 90 per cent of the 117 stillborn and newborn rabbits autopsied were contaminated with blood, epithelial cells, and amorphous debris; large areas of the alveoli and bronchioles of both lungs were involved in 40 per cent of the autopsies.

3. After normal labor, uncomplicated by deaths, the lungs of 164 newborn rabbits obtained by sacrifice of 30 litters showed only minor quantities of erythrocytes and cellular debris scattered in the air passages; there was no case of massive contamination of the lungs such as characterized 40 per cent of the autopsies of stillborn fetuses and those that died neonatally.

4. Increase in the duration of labor is linked with increase in foreign matter of the birth canal in the fetal air passages.

5. The origin of pulmonary hyaline membrane is related to fetal respiration: the entrance of fluid and cellular debris of the birth canal into the fetal air passages during labor accounts for the origin of foreign matter in the lungs of the newborn; the displacement of the eosinophilic matter in a membranelike layer along the walls of the alveoli and bronchioles results from the expansion of the air passages with the entrance of air.

6. In littermates expelled through the same birth canal, the foreign cellular debris in the lungs is strikingly similar; however, in the stillborn, its displacement in the form of a film has not occurred.

7. In the course of parturition of the type characterized by multiple births, the influence of dilatation of the air passages with the entrance of air upon the distribution of the alveolar contents stands out with exceptional detail.

8. The regular occurrence of atelectasis in areas of the lungs marked by membranelike dispersion of the foreign matter is further evidence of obstruction.

9. Asphyxia of the newborn involves more than oxygen want; in many instances there is also increase in duration of exposure to a fluid environment containing blood and bacteria with consequences that extend far beyond the time of birth.

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ACTIVE PARTICIPATION IN CHILDBIRTH*

A Psychosomatic Approach to Pregnancy and Parturition

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DR. FRED L. ADAIR[1] in his textbook, *Obstetrics and Gynecology,* defined the practice of obstetrics as "the art and science of properly caring for the fetus and the woman during the performance of childbearing to the end that the structures, functions, health, and lives of both mother and offspring may be conserved and preserved, and the best interests of the individual, the family, and the human race be furthered." While Dr. Adair did not expressly include emotional health in his definition, he was undoubtedly aware of its role in furthering the best interests of the mother, the family, and the human race.

The concept that emotions affect the woman in labor is not new. As long ago as 1888, S. C. Busey[2] wrote: "The manifestations of suffering are more influenced by mental and emotional than the physical conditions." This, however, was but a passing thought, and obstetricians went about their task of improving maternal and fetal mortality and morbidity statistics by concentrating upon the anatomical, physical, and mechanical aspects of childbirth. This improvement was necessarily and admirably done, but, for the most part, without consideration of the emotional health of the patient; and today, the obstetrician too frequently considers the parturient woman as nothing more than a mass of "double X protoplasm" from which it is his task to extract by "hook or crook" a similar, and he hopes, pink, squirming, smaller mass.

In 1944 Grantly Dick Read's book, *Childbirth Without Fear,* was published. There developed an immediate and intense interest in his concepts of physiological labor, or so-called "natural childbirth." All of this interest was not positive, however, and physicians and patients aligned themselves either for or against the concepts and procedures.[3-6] As time has passed and experience has been obtained, it becomes increasingly apparent that psychosomatic concepts are being firmly established and, as these concepts are applied to the obstetrical patient, it is no longer possible for the obstetrician who professes to care adequately for his patient to ignore the important role which emotional health plays in furthering her best interests.

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In practicing obstetrics, it is obvious that any one routine does not meet the needs of all patients. We are all familiar with the woman who attempts natural childbirth but who does not exhibit the positive reactions so often described; and the one who is given medication or anesthesia to the point of no discomfort, but who feels "not quite satisfied" or that she has "missed something of importance." Any rigid approach to pregnancy and parturition is bound to produce a greater number of these dissatisfied and unhappy mothers.

The psychosomatic approach to childbirth which this paper reports was conceived in an effort to avoid this rigidity, to include psychological preparation for labor as well as analgesia, anesthesia, outlet forceps, episiotomy, and all other aids which contribute toward achieving the best results in modern obstetrics.

Approach to the Patient

At the first prenatal visit it was pointed out that the three individuals most directly involved—the patient, her husband, and the physician—should participate in all activities and that all three should strive for a pleasant and satisfactory experience in which the mother would be in as good health, or better, at the conclusion as in the beginning of the pregnancy, with a healthy infant. There was no hesitation in suggesting that psychological factors could contribute toward this goal, that each of the participants were responsible for rather specific areas of activity, and that the degree of success would depend upon how adequately each functioned.

At this first consultation a complete obstetrical history was taken and physical examination made. The importance of proper diet and weight control was stressed. and the group instruction periods and lectures in which she could participate, if she so desired, were briefly outlined. It was stressed that her baby should be delivered in the way which suited her own needs most adequately, that she would have medication to relieve discomfort as the need or desire for it arose, and that she could have any safe type of anesthesia available.

Subsequent prenatal visits were neither unduly prolonged nor complicated. The usual prenatal check of the general physical condition was made and, in addition, any questions the patient asked were answered frankly and in as much detail as necessary. If the patient seemed tense, frightened, or emotionally disturbed, she was encouraged to "get the difficulty off her chest." She was allowed to express the emotional content of her problem freely and without embarrassment, and the physician talked as little as possible. These periods were approached as psychotherapeutic sessions and the principles of psychotherapy as discussed by Alexander and French[7] were kept in mind. In general these principles are: (1) verbalization of the problem, (2) emotional catharsis by the patient, (3) interpretation and explanation of the emotional reactions by both patient and physician, (4) reassurance by the physician, and (5) re-education of the patient's emotional reactions.

Patients who so desired atttended four group sessions which were given at regular intervals. Two classes for the patients were directed by the nurse, and two evening lectures attended by both husband and wife were given by the physician.

The first class conducted by the nurse was entitled "Body Mechanics." The material presented was designed to improve body mechanics and posture during pregnancy, and to aid the patient in practicing muscle relaxation and control.[8]

The second class conducted by the nurse had to do with specific preparation for labor techniques. Illustrations[9] were used to present information concerning the stages of labor, what the patient could expect to occur in each stage,

how she could make use of body relaxation to assist herself during the first stage of labor, and how she could work more effectively with the "bearing-down sensations" of the second stage. Questions were answered as completely as possible, and the patients were neither encouraged along the lines of natural childbirth nor encouraged to have complete anesthesia. It was stressed that each patient should have during her labor what seemed to meet her individual needs and desires most satisfactorily.

The first evening lecture was termed an "Introduction to Pregnancy." The material presented in this lecture approached the psychological aspects of pregnancy and childbirth more than that of any other part of the program. It was stressed that psychological factors, more than physical, contribute to satisfaction in pregnancy and parturition. The relationship between emotions and body functioning was discussed and it was pointed out that one must accept the concept of psychosomatic functioning of the body before the material presented would have meaning.

The material presented in this first lecture was organized under four general headings:

I. The effect of the social mores and customs of the society in which the patient lives upon her attitudes and emotions toward pregnancy and childbirth.
   A. Specific old wives' tales, horror tales, superstitions.
   B. The effect of literature; history, particularly of obstetrics; anthropology.
   C. The unconscious nature of most of this influence. The patient was encouraged to consider this material but not to be frightened by its content.

II. The effect of ignorance and lack of information concerning pregnancy and childbirth. Very briefly and with projected slides, the anatomy of the pelvis with specific relationship to pregnancy and other pertinent information were presented.

III. The effect of the psychosexual background of the patient. This area was discussed briefly and carefully.

IV. The effect of the immediate environment. It was pointed out that pregnancy and childbirth in the milieu of a happy marriage, free from economic and other environmental difficulties, would be a better-endured pregnancy.

The second discussion by the physician emphasized the labor process and the hospital situation. The stages of labor were presented by slide illustrations, and methods of muscle relaxation were reviewed. Things which the husband could do to support his wife during parturition were discussed, as were such items as when to call the physician, when to go into the hospital. A series of slides was shown depicting a patient going through labor and delivery in the hospital to which the patients would be going and introducing them to the hospital personnel.

These discussions were informal and patients and husbands frequently added comments. At times the sessions took on the characteristics of group psychotherapy and did require some skill in this area for adequate handling. Helene Deutsch's[10] contributions in the field of the psychology of women were kept in mind.

In addition to this program, several books on motherhood and childbirth were available for the patients to read.

Material and Results

Five hundred and forty-one patients were included in this study. Ten patients delivered by cesarean section were excluded from the final evaluations, leaving 531 patients from whom statistics were obtained. The patients were delivered by the same physician and an evaluation of each labor was made by him and the attending nurse at the time of delivery. The labors were evaluated according to the criteria previously suggested.[11]

TABLE I. CLASSIFICATION OF EMOTIONAL REACTIONS DURING LABOR

PARITY	NO. OF PATIENTS	CLASS I 316 PATIENTS (%)	CLASS II 206 PATIENTS (%)	CLASS III 6 PATIENTS (%)	CLASS IV 3 PATIENTS (%)	TOTAL 531 PATIENTS (%)
Primiparas	216	58	41	1.4	0.5	40.7
Multiparas	315	61	37.4	0.9	0.7	59.3
Total	531	59.5	39.0	1.0	0.6	100.0
		98.3% (522 patients) Satisfactory		1.7% (9 patients) Unsatisfactory		

Fifty-nine and five-tenths per cent of the patients made an excellent adjustment to the labor experience. This figure is not significantly different from the 56 per cent reported in 1950.[11] In the previous report, the patients had had no particular indoctrination or consistent approach to the labor experience and were delivered by different physicians. An evaluation of the percentage of patients in Class I in both reports would at first glance suggest that a psychosomatic approach to pregnancy and parturition is of little value. This is not necessarily so. It does suggest, as do other studies by Thoms,[3] Hingson,[12] Tupper,[4] and Miller,[13] that approximately this percentage of women react favorably to whatever approach is made to their childbirth experiences, and that this percentage will accept whatever approach their particular physicians choose to make. This is due more to their positive attitudes and freedom from conscious and unconscious conflicts which would influence the parturition experience negatively than to any particular skill or interest of the physician.

The interesting figure in Table I is the 39 per cent of patients in Class II. This is an increase of 7 per cent over the 32 per cent figure reported in 1950 and, when correlated with the patients' evaluation of the classes and discussions and with their positive reactions to the childbirth experience, indicates that the psychosomatic approach as outlined contributed to this improvement. A total of 98 per cent of the 531 patients were classified as having had satisfactory labors. According to the criteria of evaluation, their conduct during labor was always under control (with or without medication), they were able to rest quietly between contractions with freedom from excessive anxiety, there were no cries of terror or of pain to which they were not adjusted or from which they were not relieved; and there were no unpleasant emotional reactions post partum. These patients were cheerful, contented, pleased with themselves and their babies, and looked back upon the experience with feelings of satisfaction and accomplishment.

The 2 per cent of the patients who fell into the unsatisfactory classes were those whose unconscious, negative motivations for pregnancy and parturition were too deep and intense to respond to the psychosomatic approach, or those in whom a mistake in judgment as to medication and anesthesia was made by the physician.

Table II indicates the medication and anesthesia received by the patients.

TABLE II. ANESTHESIA AND MEDICATION

	315 MULTIPARAS (%)	216 PRIMIPARAS (%)
Anesthesia.—		
None	2	4
Pudendal block	78	65
Pudendal block and ether	9	10
Ether	8	14
Spinal	1	2
Nitrous oxide or Trilene	2	5
Medication Before Delivery.—		
None	1	2
Demerol, 50 to 100 mg.	62	70
Demerol, 150 to 250 mg.	19	3
Demerol, 300 mg. or more	6	2
Thorazine, 25 mg., plus Nisentil, 40 to 80 mg.	12	23

As indicated, 2 per cent of the primiparous and 4 per cent of the multiparous patients received no anesthesia for delivery. Eighty-seven per cent of the primiparous and 75 per cent of the multiparous patients had pudendal block anesthesia or pudendal block anesthesia with a few whiffs of ether with the delivery of the head and shoulders. The solution for the pudendal block anesthesia consisted of 1 per cent Novocain to which 150 units of hyaluronidase and 3 minims of 1:1,000 epinephrine were added. Approximately 30 c.c. of this solution sufficed for the entire anesthesia. There were no untoward reactions to this anesthesia in any patient.

Sixty-two per cent of the primiparas and 70 per cent of the multiparas received minimal amounts of Demerol for analgesia. Since the introduction of chlorpromazine in obstetrics, a dose of 25 mg. has been given intramuscularly early in labor. This contributed to the relaxation of the patient and to reduction in the amount of narcotic used. The patient usually asked for narcotic medication when the cervix was 6 to 8 cm. dilated and rarely were requests made for additional medication.

These statistics are not as good as those of other reports. This is not a particularly important point of difference, however. It is important that the parturient woman should not receive excessive medication or unsafe anesthesia. This psychosomatic approach to childbirth contributed to a more flexible and safer application of this principle.

TABLE III. LENGTH OF LABORS

LENGTH (HOURS)	NO. OF PATIENTS	315 MULTIPARAS (%)	216 PRIMIPARAS (%)
Under 3	65	18.0	4.0
3 to 6	138	35.0	12.5
6 to 12	185	32.0	39.0
12 to 18	88	9.0	27.0
18 to 24	34	3.0	11.0
Over 24	21	2.5	6.0

Table III shows the length of the labors experienced by the 531 patients. The table indicates that 85 per cent of the multiparas and 55.5 per cent of the primiparas experienced labors of 12 hours or under in length. Only 8.5 per cent of all patients had prolonged labors. Smooth, progressive, relatively short labors add to the satisfaction experienced by a woman in labor, and tend

to minimize the need for medication and deep anesthesia. Whether or not a psychosomatic approach to childbirth shortens the labor is not as important as that the patient knows more what to expect, is able to apply techniques which decrease the discomfort, and, because she has some understanding of her own motivations and emotional reactions, is better able to control the anxieties which are common to all women in childbirth.

TABLE IV. TYPE OF DELIVERY AND LACERATIONS

	216 PRIMIPARAS (%)	315 MULTIPARAS (%)
Delivery.—		
Spontaneous	43	71
Outlet forceps	56	28
Midforceps	1	1*
Episiotomy	93	50
Lacerations.—		
First-degree perineal	2	10
Second-degree perineal	2	5
Third-degree perineal	1	0
Vaginal	5	0.6

*One infant in this group was delivered with high forceps.

Table IV gives the incidence of forceps and spontaneous deliveries, episiotomies, and lacerations which occurred in the 531 deliveries.

There is no particular virtue in a minimal use of the outlet forceps to deliver the infant's head. Since De Lee first suggested their use as a means of protecting the perineum and avoiding often unrecognized damage to its submucosal and deeper tissues, they have been found to be of value.

So, too, has the value of the episiotomy been accepted. This study indicates that, as the patient took a more active part in the delivery process, and when pudendal block anesthesia was used, low forceps, applied gently with minimal traction concomitant with the uterine contraction, could be used without resort to general anesthesia.

The interesting figures in Table IV are those which indicate the infrequent use of midforceps and the infrequent incidence of perineal and vaginal lacerations. They indicate that the woman who works actively and effectively with her second-stage contractions, and who requires a minimum of medication and anesthesia, sets the stage for fewer complications at the time of delivery.

TABLE V. ESTIMATED BLOOD LOSS

BLOOD LOSS (C.C.)	216 PRIMIPARAS (%)	315 MULTIPARAS (%)
Up to 100	17	20
101 to 200	63	57
201 to 300	15	15
301 to 499	2	7
Over 500	3	1

Table V gives the estimated blood loss which occurred during the 531 deliveries. This is admittedly an inaccurate method of reporting blood loss, and the statistics, except for blood loss over 300 c.c., are only approximate. Repeated checks were made, however, and the estimations were consistently within 50 to 75 c.c. of measured amounts. Blood loss of 300 c.c. or over was always measured. If the figure of 250 c.c. is accepted as the average blood loss during labor and the delivery of an infant, these patients lost at least as little blood as the average, and probably less than those who received spinal or general anesthetics.

The low incidence of postpartum hemorrhage is more striking. Vant,[14] discussing postpartum blood loss in an analysis of 6,000 cases, reported an incidence of 4.3 per cent in which hemorrhage of more than 600 c.c. occurred. The lower incidence of postpartum hemorrhage and the decreased blood loss at the time of delivery in the 531 patients reported in this study were probably due to the same factors which decreased complications in general, i.e., shorter labors, less medication, fewer general anesthetics, and the all-around general good health evidenced by patients relatively free from the effects of negative emotions on their pregnancy and childbirth experiences.

All 531 patients were sent an evaluation sheet upon which they were asked to evaluate the various factors in this psychosomatic approach to their pregnancies and labors. Four hundred and sixty-eight, or 86.3 per cent of the patients returned the sheets. Table VI lists the nine most frequently mentioned factors which contributed most to their satisfaction in labor.

TABLE VI. FACTORS CONTRIBUTING TO SATISFACTION IN LABOR

	196 PRIMIPARAS (%)	272 MULTIPARAS (%)
Being awake during labor and delivery	74	97
Abdominal breathing during first-stage contractions	63	72
General body relaxation between contractions	33	38
Husband in labor room	29	28
Predelivery medication	21	26
Confidence in the doctor	9	--
Being asleep or having spinal anesthetic for delivery	5	3
Understanding care of nurses	5	6
Knowing that the doctor is in the hospital and available before being taken to the delivery room	5	5

It is interesting to note that 74 per cent of the primiparas and 97 per cent of the multiparas indicated that being awake during the delivery of the baby provided them with the greatest satisfaction. Many of these patients commented that the childbirth experience was the most satisfying and thrilling experience of their lives, and that they were anticipating with pleasure their next pregnancy. Fifteen per cent of the multiparas commented that this labor experience had erased "unpleasant," and even "horrible," memories of previous labors and that they were grateful to be able to anticipate subsequent labors pleasantly. Many primiparas stated that, while they were relaxed, there still was some discomfort and they appreciated the predelivery medication given. These patients also mentioned the pleasure and satisfaction of accomplishment which they felt at the time of delivery.

The simple procedure of abdominal breathing was listed next most frequently, followed by general body relaxation as important factors contributing toward relief of discomfort. Including the husband in the prenatal care and allowing him in the labor room was listed fourth, ahead of medication which did not appear until fifth on the list. Only 5 per cent of the primiparas and 3 per cent of the multiparas specifically mentioned being asleep or spinal anesthesia as contributing most to satisfaction during labor.

Table VII indicates the patients' evaluation of the classes, lectures, and the hospital tour.

The patients were asked to evaluate the five sessions from 1 to 5—1 indicating the most valuable and 5 the least valuable. Only those evaluated as 1 are included in the table. The physician's discussion on labor and the hospital was most frequently placed in the No. 1 category by both primiparas and

multiparas. A large number of patients stated that all of the classes and lectures and the hospital tour were of equal value. Only a few patients evaluated any of the classes or lectures as low as 5, and it is reasonable to conclude that these patients were those who had unsatisfactory labors.

TABLE VII. PATIENTS' EVALUATION OF LECTURES, CLASSES, AND HOSPITAL TOUR

	196 PRIMIPARAS (%)	272 MULTIPARAS (%)
Physician's lecture on hospital and labor	81	76
Preparation for labor class	59	57
Hospital tour	55	34
Physician's introduction to pregnancy lecture	51	50
Body mechanics class	46	43

The patients were also asked for suggestions as to how their labor experiences could be made more satisfying. Forty and five-tenths per cent of the patients who responded to the questionnaire felt that having their husbands in the delivery room where they could share the experience of childbirth together, and where the husband could add moral support would be a distinct advantage. Throughout the country at the present time this is a controversial point with physicians and hospital personnel. There are arguments for and against having the husband in the delivery room. Some are valid and some are not, but as more parturients remain awake during the delivery of their babies and experience a positive emotional reaction, there is going to be an increasing demand for the husband to be with his wife. This will change the atmosphere of the delivery room and require more of the physician's time during the terminal portion of labor. It will also require more appreciation and application of the psychosomatic aspects of childbirth than are now current.

Less frequently mentioned factors which the patients felt would aid in making another labor more satisfying were: (1) more regular attendance at the lectures and classes, (2) more diligent practice of the relaxation exercises, (3) more understanding of and explanation as to the progress being made in labor by those attending the patient, (4) more opportunity for moral support and help from the husband, and (5) the presence of the physician during more of the labor.

The patients were also asked to list their anxieties and worries during pregnancy and labor. Twenty-nine per cent of primiparas and 28 per cent of multiparas specifically stated that there were none during pregnancy, while 27 per cent and 24 per cent listed none during labor. These are doubtful statistics. Helene Deutsch[10] stated that there are anxieties, some of which are of the unconscious variety, common to all women during the labor experience and pregnancy. These doubtful statistics are best explained by the patients who stated that they had anxieties and worries, but that the prenatal program either eliminated them or reduced their intensity sufficiently to make it possible for the patients to keep them under control.

Specific anxiety factors most frequently listed by those aware of anxieties and fears were: (1) fear of an abnormal or injured baby, (2) fear of injury or harm to self—fear of death, pain, long labor, too rapid labor, (3) fear of complications such as Rh sensitivity, abortion, false labor, not reaching the hospital in sufficient time for delivery of the infant, and (4) fear of hospital routine. These factors have been discussed frequently by other writers, and are discussed in detail by Deutsch.[10] The majority of patients felt that, even though anxieties and fears were present, the information and reassurance gained from the psychosomatic approach to the prenatal care helped in understanding and controlling them.

During pregnancy and parturition, the anxieties of the mother concern either herself or her infant. The obstetrician also must always consider both. During this study there were 13 fetal deaths in 541 deliveries. Table VIII lists these deaths and the probable cause of death. The material is self-explanatory.

TABLE VIII. THIRTEEN FETAL DEATHS IN A TOTAL OF 541 PATIENTS

PATIENT	PARITY	DELIVERY	COMPLICATIONS AND CAUSE OF FETAL DEATH
L. D.	Primipara	Vaginal	Abruptio placentae; premature infant weighing 4 pounds; congenital atelectasis
P. E.	Primipara	Vaginal	Partial separation of placenta; premature infant weighing 5 pounds; hyaline membrane disease
A. A.	Primipara	Vaginal	Premature twins at 25 weeks' gestation; prematurity
D. B.	Multipara	Vaginal	Erythroblastosis fetalis; hydropic infant
N. P.	Multipara	Vaginal	Erythroblastosis fetalis
B. T.	Multipara	Vaginal	Erythroblastosis fetalis
V. S.	Primipara	Cesarean section	Mother had severe diabetes with uncontrollable pre-eclampsia; cesarean section at 32 weeks' gestation; premature infant with multiple congenital abnormalities
B. C.	Multipara	Vaginal	Premature delivery; breech presentation with prolapsed cord; infant weighed 2½ pounds. No autopsy
W. F.	Multipara	Vaginal	Premature infant weighing 4 pounds, 3 ounces; congenital atelectasis and pulmonary hyaline membrane disease
Y. M.	Multipara	Cesarean section	Premature separation of the placenta; term infant; congenital atelectasis
M. O.	Multipara	Vaginal	Term infant; immature development; probable congenital atelectasis. No autopsy
C. M.	Multipara	Cesarean section	Premature separation of the placenta; premature infant weighing 5 pounds; congenital atelectasis

Comments

The problem of applying psychological as well as physical, anatomical, and mechanical concepts in the care of the obstetrical patient is twofold. The psychological concepts must first be accepted by the physician and the patient, and then they must be practically applied. Just as Semmelweis, the Father of Aseptic Obstetrics, was rejected and ridiculed for his approach to the problem of childbed fever; so Philippe Pinel, the Father of Therapeutic Psychiatry, was berated and stoned in the streets of Paris for his approach to psychiatric patients. Today, while everyone accepts Semmelweis' contribution to the practice of obstetrics, too many refuse to accept the role that psychological and emotional factors play.

The refusal to accept the fact that emotions influence the course of pregnancy and parturition is due to the unconscious nature of psychological components of the personality. It is in the unconscious that such severe conflicts as rejection of sex and femininity, hostility toward the mother figure, and conflicts between masculinity and femininity exist. They can be more intense and more difficult to approach than conscious factors but are nonetheless important and powerful in their influence upon the obstetrical patient. The effects of these conflicts were aptly expressed by Menninger[15] when he wrote: "From investigations into the unconscious we have learned that an individual may consciously express one attitude, wish or intention, while unconsciously harboring an entirely different or even opposite one. Since the individual does function as a total unit we may expect that there will be some evidences expressed not only

psychologically but physically, of the presence of such conflicting wishes.'' The failure to recognize the importance of the psychological and emotional aspects of childbirth and the failure to apply the information which is known are the areas in which most physicians are lacking in the practice of obstetrics.

This does not mean that the concepts of good obstetrics based upon a knowledge of the basic sciences are not important. In stressing them, however, the emotional and psychological needs of the patient should not be ignored. At the same time, the physician must understand and recognize his own personality needs and motivating forces, both conscious and unconscious, and realize that they also influence the childbirth experience. A knowledge of psychiatry, and of one's self, makes it easier for the physician to use psychosomatic concepts in a total approach to the obstetrical patient.

Another deterring factor in the application of psychosomatic concepts to childbirth is the failure of some hospital personnel to understand the approach. It is possible for some of these individuals to be unaware of their own personality needs and unconscious conflicts which determine their approach to the woman in labor. As a result, they give less than completely sympathetic and understanding care. Hospital administrators and other personnel, for the same reasons, or because they lack courage to approach something new, resist change in established concepts and routines. These factors have been pointed out by others, and time and education will minimize this negative influence.

This study indicates that when the pregnant woman, her husband, and the physician consider the psychosomatic aspects of pregnancy and childbirth a larger number of patients adjust more adequately to the anxieties and discomforts of the experience. Admittedly, the evaluation of this approach involves subjective elements, and control groups are difficult to formulate. There is a general definite impression, however, that the reduction in the amounts of analgesia and anesthesia used, the incidence of shorter labors, less damage to maternal tissues, lower incidence of the application of midforceps, less blood loss, and the lower incidence of hemorrhage, make it worthy of consideration by the obstetrician.

Just as important as these advantages is the tremendously satisfying, positive emotional reactions of the patients. Parks[16] stated: ''Obstetricians and gynecologists have unusual opportunities to direct patients in healthy attitudes regarding sex, childbirth, and parenthood. . . . While we must maintain a diligent respect for the serious complications which can occur in pregnancy, it is our duty, responsibility, and pleasure as physicians to convey a feeling of security, happiness, and well being, as free from all fears as possible, in the new mother-to-be. . . .'' In no other project do two individuals collaborate more completely intellectually, physically, and emotionally, than do a husband and wife in the production of their infant. The physician who joins the project as adviser, protector of health, and assistant, by taking an active part in furthering positive attitudes, can do more toward the development of a happy, worthwhile marriage and a home in which healthy, well-adjusted children reside than any other individual. This is his responsibility, and it is his destiny.

Summary

1. The importance of considering the emotional and psychological aspects of pregnancy and parturition is presented.

2. A psychosomatic approach to pregnancy and childbirth is outlined and the results of its application to 531 patients are presented and discussed.

3. It is concluded that a complete approach to pregnancy and parturition should include the psychosomatic aspects.

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PREVENTION OF PREMATURE DELIVERY

Therapeutic Results in 76 Patients

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SINCE prematurity causes over half of all perinatal infant deaths, methods of preventing premature labor and delivery appear to hold the greatest hope for reducing mortality at this crucial period.

Davis, Potter, and Bruce[1] used "perinatal mortality" as a comprehensive term including death just before, during, and just after birth, since these are areas of prime obstetric responsibility. Gold[2] defined perinatal mortality as infant deaths (under 1 week) and late fetal deaths (over 28 weeks' gestation). He noted, in collecting statistics for the years 1946 through 1953 for the city of New York, that there was a decline in the over-all perinatal mortality rate of 19.5 per cent. The fetal deaths (28 weeks and over) declined 28.0 per cent, and the early infant deaths (under 7 days) declined 12.0 per cent. The maternal mortality rate declined 44.4 per cent for the same period. Ninety per cent of the early infant deaths were due to perinatal causes, namely, prematurity in 51 per cent, birth injuries and malformations in about 15 per cent each, and anoxia and erythroblastosis in 11 per cent.

Bundesen[3] reported that 79.1 per cent of natal day deaths in Chicago are the result of prematurity. The incidence of prematurity in New York City during the years studied by Gold (1946 through 1953) has remained fairly constant at a level of 8.1 per cent of all live births, with an incidence of 7.5 per cent in the white as compared to 11.5 per cent in the nonwhite population. Thus it seems obvious that further reduction of perinatal mortality is keyed to reduction in premature delivery.

The first step in this reduction rests with recognition of the impending premature onset of labor and delivery. It was found that premature delivery could be predicted and an estimation made of the time when labor could be expected to start, by changes in the cervix. These changes were determined by vaginal examinations under sterile precautions of all obstetrical patients at every office visit and as a routine during labor. Previous concern over the use of sterile vaginal examination has proved groundless.[4-7] During this 9 years' investigation, labor has not been induced prematurely, nor have other problems arisen from these examinations.

It became evident very early in the study that premature delivery was always preceded by an extended period of preparation of the cervix and lower uterine segment, similar to the changes which take place before normal full-term deliveries (Figs. 1 and 2). An estimation of the state of the cervix at each examination was recorded.

Method

The cervix was measured in its three important aspects: The external os, the internal os, and the thickness. These measurements were recorded numerically in centimeters. A notation of 0-0-4 means that the cervical canal was closed normally at the external os and also at the internal os and the cervix was 4 cm. in thickness. Similarly, 1.5-0.5-2.0 would mean the external os was dilated 1.5 cm. in diameter, the internal os 0.5 cm., and the cervix was 2 cm. thick.

During the early period of this study, hormones (e.g., stilbesterol, progesterone, thyroid, etc.) were used in combination with antibiotics, sedation, and bed rest, in an attempt to arrest or delay premature delivery without appreciable success. Thyroid and antibiotics where specifically indicated have, of course, proved useful.

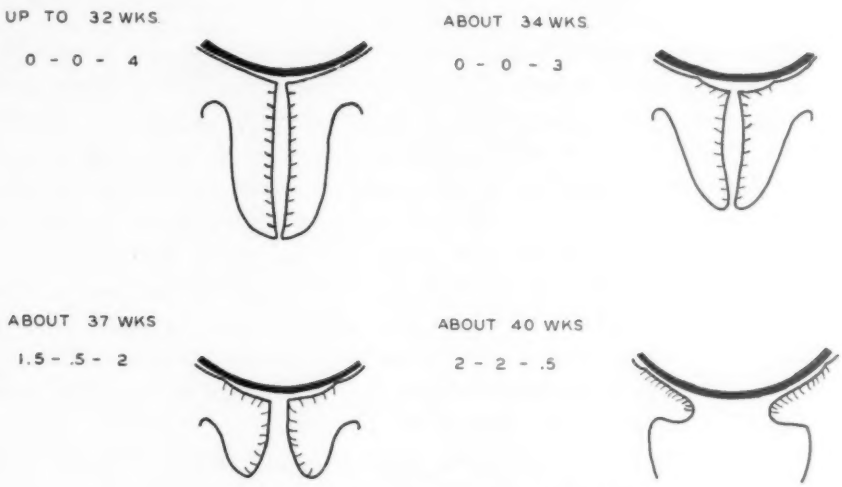

Fig. 1.—Cervix of a typical primigravida.

In the search for more effective agents, it was hoped that some of the newer anticholinergic substances might offer some help in the prevention of uterine contractions as indicated in a previous publication.[9] Most of the anticholinergics studied proved unsatisfactory in this condition. I noted, however, that N-ethyl-3-piperidyl diphenylacetate hydrochloride (Dactil*) was effective in preventing the onset of labor in cases where there was thinning and/or dilatation of the cervix. If the patient had not yet reached the point of actual labor, Dactil seemed to diminish spasms of the uterine muscle.

Dactil therapy has been used in this study as a preventive measure as well as in the management of premature delivery. The usual dosage of Dactil was 50 to 100 mg. four times a day, administered orally. Treatment was initiated as soon as the diagnosis of possible premature delivery was made and was continued until the thirty-ninth week of gestation or until delivery. No side effects were observed with Dactil therapy. While in most cases it was found possible to prolong the prenatal period with Dactil until near or at term, in some instances, where uterine contractions indicated imminent delivery, it was felt desirable to supplement the oral Dactil with a parenteral anticholinergic.

*Lakeside Laboratories, Inc. "Dectil is an anti-cholinergic drug which exhibits post-ganglionic, parasympathetic depressive action, particularly at the myoneural junction of the upper gastro-intestinal tract and very likely at other autonomic levels. The rationale of its use is based upon activity in blocking acetylcholine at the smooth muscle myoneural junction, but not at the ganglionic level. There is a definite, but mild musculo-skeletal relaxing effect, 'curare-like,' presumably due to its piperidol chemical structure."

Dibutoline sulfate (Dibuline*) in dosages of 25 to 50 mg. hypodermically possesses a definite blocking action on uterine contractions and has been used successfully to stop the more violent contractions even when the patient was actually in labor. Dibuline has an atorpine-like action on the eyes, with some blurring of vision, and a marked drying effect on the mouth. It produces such a marked blocking action that repeated use to keep labor in abeyance may produce constipation and even bladder atony. The patient tends to accept these side effects without complaint, however, when it is realized that the medication may prove to be a means of preventing premature delivery. Dibuline was used only as needed to stop contractions and not as a preventive measure. No abnormalities, either maternal or fetal, were noted as a result of the administration of Dactil or Dibuline.

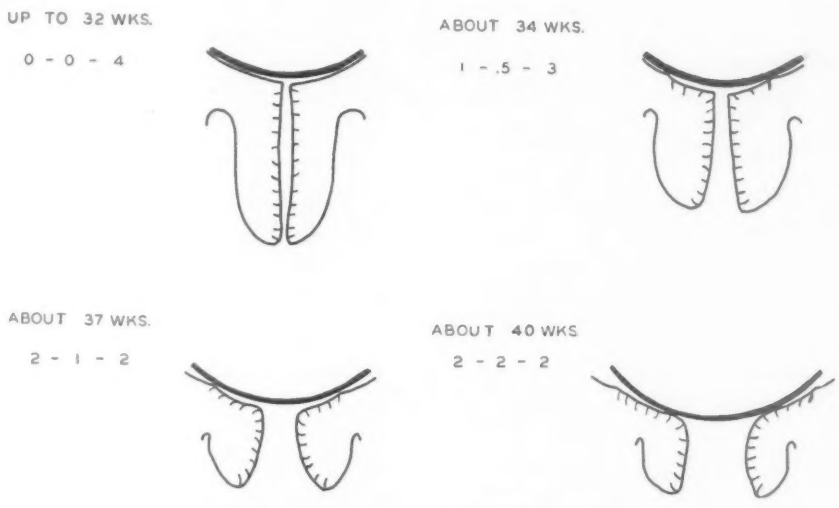

Fig. 2.—Cervix of a typical multigravida.

Results

This report covers 76 patients who have been treated in private practice with Dactil during 81 pregnancies, all of them considered probable candidates for premature delivery. Fifty-seven of these patients had been followed prior to the Dactil study for a total of 102 pregnancies and had been given whatever therapy seemed best at the time, such as hormones, bed rest, and sedation. These same 57 patients have now been observed under Dactil therapy during 62 additional pregnancies which included 6 pairs of twins and one set of triplets.

Dactil therapy was initiated routinely and continued through the thirty-ninth week of gestation or until delivery under any one or more of the following conditions: 1. Cervical dilatation and/or thinning before the thirty-second week of gestation. 2. A definite history of premature delivery or spontaneous abortion. 3. Diagnosis of multiple pregnancy. 4. Uterine cramping or bleeding.

The relationship between premature dilatation of the cervix and premature delivery has been previously noted. This relationship is borne out by Table I,

*Merck Sharp and Dohme Laboratories. Dibuline is available only in the injectable form in 5 c.c. multiple-dose vials containing 25 mg. per cubic centimeter.

covering 39 patients with a total of 109 pregnancies. In pregnancies prior to Dactil therapy there were 21 abortions; 18 cases of premature dilatation of the cervix; and only 30 of normal dilatation. The data in this table are significant. The patients selected were those who had had continued difficulty in bearing full-term living infants and who had been treated previously with whatever drug was at hand. Discounting the abortions, in the 30 cases of normal dilatation the infants averaged 7 pounds, 2 ounces in weight, whereas in the 18 cases of premature cervical dilatation they averaged only 5 pounds, 8¾ ounces.

TABLE I. OBSTETRICAL HISTORY OF 39 PATIENTS RELATED TO WEIGHT OF BABIES

	PRIOR PREGNANCIES	AVERAGE WEIGHT OF BABIES	PREGNANCIES WITH DACTIL THERAPY	AVERAGE WEIGHT OF BABIES
Abortions	21		1	
Normal dilatation*	30	7 pounds, 2 ounces	3	6 pounds, 9½ ounces
Premature dilatation	18	5 pounds, 8¾ ounces	36	6 pounds, 11 ounces
Total pregnancies	69		40	

*Dilatation began at 32 weeks or later.

In contrast, in the same 39 patients who later received Dactil therapy during their 40 pregnancies, 36 of which were accompanied by premature dilatation of the cervix, the mean weight of the babies was 6 pounds, 11 ounces. Also, the mean weight of the babies delivered by the 3 patients who had no premature dilatation of the cervix was 6 pounds, 9½ ounces. There was only one abortion in this group. Thus, patients with premature dilatation of the cervix when treated with Dactil gave birth to babies with a mean weight 1 pound higher than with previous management.

TABLE II. OBSTETRICAL HISTORY OF 57 PATIENTS RELATED TO WEIGHT OF BABIES

	PRIOR PREGNANCIES	AVERAGE WEIGHT OF BABIES	PREGNANCIES WITH DACTIL PLUS DIBULINE THERAPY	AVERAGE WEIGHT OF BABIES
Abortions	36		1	
Normal dilatation*	44	7 pounds, 1½ ounces	4	6 pounds, 11¾ ounces
Premature dilatation	27	5 pounds, 11 ounces	57	6 pounds, 7 ounces
Total pregnancies	107		62	

*Dilatation began at 32 weeks or later.

Table II presents data from Table I and includes an additional 18 patients who were treated with oral Dactil plus Dibuline. Again, the large number of abortions (36) and premature dilatations (27) is obvious. Also, the difference between the birth weights resulting from pregnancies with normal dilatation (7 pounds, 1½ ounces) as compared to those where dilatation occurred prematurely (5 pounds, 11 ounces) is appreciable. In the group treated with the anticholinergic drugs, 57 patients in whom the cervix dilated prematurely had babies with a mean weight of 6 pounds, 7 ounces, as against a mean weight of 5 pounds, 11 ounces of the 27 infants delivered by the same mothers previously without anticholinergic treatment. Again there was only one abortion in the group who received anticholinergic drugs.

Table III includes all the 76 patients treated *with* Dactil and Dactil plus Dibuline. It is a composite of the same 57 patients discussed above, plus an

additional 19 patients whose previous pregnancy histories were unavailable. It is notable that 68 pregnancies with abnormal premature dilatation resulted in babies averaging 6 pounds, 8½ ounces in weight following therapy. This is even more important from the standpoint, as previously mentioned, of the extreme likelihood of premature delivery in all these cases. Six pounds, eight and one-half ounces is a very respectable average birth weight for these babies.

TABLE III. OBSTETRICAL HISTORY OF PATIENTS TREATED WITH DACTIL AND/OR DIBULINE

	DACTIL TREATED	AVERAGE WEIGHT OF BABIES	DACTIL-DIBULINE TREATED	AVERAGE WEIGHT OF BABIES	TOTAL TREATED	
Abortions	1		0		1	
Normal dilatation*	9	6 pounds, 14½ ounces	3	7 pounds	12	6 pounds, 14¾ ounces
Premature dilatation	44	6 pounds, 12 ounces	24	6 pounds, 3 ounces	68	6 pounds, 8½ ounces
Total pregnancies	54		27		81	
Total patients	53		26		76	

*Dilatation began at 32 weeks or later.

Table IV presents all cases of multiple pregnancies (7) treated by the author since initiation of Dactil therapy. These pregnancies were treated with Dactil from the time of diagnosis of multiple pregnancy until delivery.

TABLE IV. MULTIPLE BIRTHS OF DACTIL-TREATED PATIENTS

PATIENT	CERVICAL DILATATION BEGAN (WEEKS)	DACTIL THERAPY BEGAN (WEEKS)	GESTATION (WEEKS)	WEIGHTS OF BABIES					
				BABY 1		BABY 2		BABY 3	
				POUNDS	OUNCES	POUNDS	OUNCES	POUNDS	OUNCES
K. B.	16	33	40	5	15	6	13	6	3
P. M.	19	19	38	7	8½	7	5		
M. McG.	36	36	39	5	4	5	1		
C. F.	--	30	36	4	7	4	12		
M. M.*	21	29	36	5	3	5	7		
B. L.*†	26	33	38	5	11	5	11		
L. M.	20	29	37	7	3¾	7	9		

*Also given dibuline.
†Cesarean section.

M. M. and B. L. had both Dactil and Dibuline. M. M. had spontaneous rupture of the membranes 4 weeks prior to delivery. She was maintained at bed rest in the hospital and treated with antibiotics, Dactil, and Dibuline. In the case of C. F., labor began and she was delivered 24 hours after the spontaneous rupture of the membranes in spite of the treatment. In the case of M. McG., Dactil was not started until the thirty-sixth week, because she failed to come in for earlier care.

While statistics are valuable and revealing, they sometimes fail to portray the complete picture. Some interesting observations appeared which are not adequately illustrated by the statistical tables.

A typical case is that of J. C., hospital laboratory technician. Her first pregnancy at age 27 appeared normal in every way until, at routine examination at the twenty-second

week, the cervix was found to be dilated 1 cm. at the external os and to be 4 cm. in thickness. By the twenty-sixth week she was having recognizable uterine contractions and the cervix was 2-2-3. She was advised to stay in bed at least one-half hour out of each hour during the day. By the thirtieth week the cervix was 2-2-2. She was still having some uterine contractions. At the thirty-third week the cervix was dilated 3-3-2, the head was presenting and engaged in the pelvis. Uterine contractions were continuing. She was advised to start complete bed rest. At the thirty-ninth week the cervix was dilated 5-5-0.5. At the fortieth week she went into spontaneous labor, and after 2 hours, 20 minutes of mild labor delivered a 7 pound, 4½ ounce boy.

With her second pregnancy at the age of 29, she was first seen at the sixteenth week at which time the cervix was already dilated 1-1-4 and she was complaining of uterine contractions. She was advised to start bed rest one half hour out of each hour. In spite of this, by the twentieth week, the cervix was 2-2-3 and contractions were continuing, so she was placed on complete bed rest. At the twenty-seventh week, the cervix was 4-4-1 with the head engaged in the pelvis. Labor started spontaneously at 35 weeks with spontaneous rupture of the membranes. Delivery followed 2 hours and 20 minutes of mild labor. The baby girl weighed 5 pounds, 14 ounces.

At age 30, one year later, she had a spontaneous abortion at 6 weeks. At age 33 she was seen at the fourth week of gestation complaining of nearly constant cramping. She was started on Dactil, 50 mg. four times a day, and advised to take 100 mg. if needed to stop the cramping. The cervix was 0-0-4. At the eighth week the cervix was 0.5-0-4 and she was having occasional cramps, but stated they were quite well controlled as long as she continued her Dactil. At the twenty-first week the cervix was 1-0-4. She stated that she had occasional cramps which were usually controlled by lying down or by increasing Dactil to 100 mg. four times a day. She was advised to continue on the 100 mg. dosage of Dactil four times a day. At the twenty-sixth week the cervix was dilated 2-2-2. The patient was continuing to do part-time laboratory technician's work at the hospital and care for her two children at home. There were only occasional cramps. By the thirtieth week the cervix was dilated 3-3-1. She now stated she had been lying down off and on during the day but was continuing to cook and care for her family. At the thirty-seventh week, the patient noted slow leakage of amniotic fluid. She was hospitalized and placed at bed rest. Dactil was continued, and antibiotics were given prophylactically. Twenty-four hours later spontaneous labor began, and after 2 hours and 40 minutes, a boy weighing 6 pounds, 12 ounces was delivered.

Statistically, this case shows a baby nearly a pound larger and 2 weeks more mature with Dactil therapy than the previous baby. A fact more noticeable to the patient, however, is the lack of uterine contractions and the ability to continue fairly normal activity in place of forced bed rest for several weeks.

I believe that the best results of all the study are shown in the cases of the 7 multiple pregnancies where the sizes of the babies are unusually large. More gratifying yet is the fact that, out of the 7 cases, the entire number seen during the 2 year study, not one pregnancy or baby was lost.

Summary

Routine serial observations of cervical changes throughout pregnancy have proved valuable. These studies of cervical changes in conjunction with the usual prenatal observations may be used to predict premature labor. Two anticholinergic drugs have proved effective in delaying imminent premature labor as evaluated in 76 women during 81 pregnancies. Dactil has been used as a preventive measure with great success and with no untoward effects.

Dibuline may be used in extreme conditions to arrest uterine contractions but is limited by the undesirable side effects and parenteral administration. It should be limited to hospital use.

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A STUDY OF 812 GRAND MULTIPARAS

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THE purpose of this paper is to review the records of 812 grand multiparous patients delivered at the District of Columbia General Hospital from 1951 through 1955. A grand multiparous woman is defined as having had eight or more viable gestations.

This is a study of a large series coming from a single teaching hospital during the period since blood transfusions, antibiotics, and fibrinogen have been available. In addition, an accurate comparison has been made with the incidence of complications in our over-all clinic group under the same obstetrical management. There were no private patients in the series.

Material

Of the 19,214 deliveries at the District of Columbia General Hospital during the period studied, there were 812 grand multiparas, an incidence of 4.2 per cent. In the series and in the over-all clinic group the race distribution was the same, 95 per cent Negro and 5 per cent white. Only 53 per cent of the grand multiparous patients received prenatal care as compared with 57 per cent in the total clinic group. The parity, age, and weight distribution are outlined in Table I.

TABLE I. PARITY, AGE, AND WEIGHT DISTRIBUTION AMONG 812 GRAND MULTIPARAS

Age.—						
Years	22-25	26-30	31-35	36-40	41-46	
%	3	25	35	28	9	
Parity.—						
Number	viii	ix	x	xi	xii	xiii-xvii
%	38	24	17	10	5	6
Weight of Patient.—						
Pounds	100-150	151-175	176-200	201-250	251 or more	
%	30	30	22	15	3	

Maternal Complications

The significant increase in maternal complications in the grand multiparous patients as compared to the over-all clinic group is shown in Table II. The incidence of abnormal presentations was more than doubled. Twins were almost twice as common. Prolapse of the umbilical cord occurred three times as often in the grand multiparas as it did in the over-all clinic group. Placental separation was more than three times as frequent. The only 3 patients in the series who developed hypofibrinogenemia had abruptio placentae. Nine of the 20 stillbirths occurred in association with abruptio placentae.

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TABLE II. COMPARATIVE STATISTICS OF MATERNAL COMPLICATIONS

	812 GRAND MULTIPARAS		19,214 PATIENTS IN GENERAL CLINIC GROUP	
	NO. OF PATIENTS	%	NO. OF PATIENTS	%
Abnormal presentations	63	7.8	751	3.9
Breech	50	6.2	625	3.3
Others (transverse 7, compound 3, face 3)	13	1.6	126	0.7
Twins	21	2.6	284	1.5
Prolapsed cord	7	0.9	51	0.3
Antepartum bleeding				
Placental separation	24	3.0	167	0.9
Placenta previa	5	0.6	154	0.8
Postpartum hemorrhage (500 c.c. or more)	19	2.3	291	1.5
Atony	11	1.4	143	0.7
Others (retained placental fragments 5, retained placenta 2, rupture of uterus 1)	8	1.0	148	0.8
Cesarean sections	31	3.8	539	2.8
Cesarean sections in multiparas for other than repeat section	24	3.0	195	1.0
Hypertensive vascular disease	179	22.1	2,459	12.8
Puerperal morbidity	24	3.0	778	4.0
Maternal death	1	0.1	18	0.09

There were 2 postpartum hysterectomies in the grand multiparous group. Both of these patients had placental separation. One had massive postpartum hemorrhage and the other had a rupture of the uterus following a breech extraction. One other rupture of the lower uterine segment was diagnosed on vaginal examination following a difficult delivery of a 10 pound, 5 ounce infant, but no surgical treatment was required.

Contrary to expectation, the incidence of placenta previa was no higher than in the general clinic group. The incidence of postpartum hemorrhage due to atony was doubled.

Eliminating the repeat cesarean sections from the grand multiparas and total clinic groups, the incidence of cesarean sections in the grand multiparas was three times that in the general clinic multiparas. The indications for the 31 cesarean sections performed are listed in Table III. It is noted that grand multiparity is no guarantee against cephalopelvic disproportion as shown by the 4 cesarean sections done for that indication.

TABLE III. INDICATIONS FOR CESAREAN SECTION IN 31 GRAND MULTIPARAS

Abnormal presentation (transverse 4, face 3, large breech 2)	9
Repeat cesarean section	7
Cephalopelvic disproportion	4
Placenta previa	3
Placental separation	2
Prolapsed cord	1
Conglutination of the cervix	1
Severe pre-eclampsia	1

The duration of labor was under 6 hours in 48 per cent of the grand multiparas, but more than 12 hours in 22 per cent.

Postpartum morbidity was about the same as in the general clinic group.

Hypertensive vascular disease was present in 179 of these 812 grand multiparas or in 22.1 per cent of the series, almost twice the incidence in the general clinic group. Obesity was a common problem, since 18 per cent of these patients weighed over 200 pounds. Table IV shows the correlation between

obesity and hypertensive vascular disease and also shows the increased percentage of hypertension in the older age group. It appears that grand multiparity was a factor in hypertensive vascular disease since, in all age groups considered, the incidence of hypertensive vascular disease was substantially greater than the clinic average of 12.8 per cent. This could not be proved, however, since equivalent age groups of the general clinic patients were not studied separately. There were no patients with eclampsia among the grand multiparas. It was impossible to ascertain accurately whether or not the patients with essential hypertension had some superimposed pre-eclampsia.

TABLE IV. HYPERTENSIVE DISEASE IN THE 812 GRAND MULTIPARAS RELATED TO AGE AND WEIGHT

Age.—				
Years	Under 31	31-35	36-40	41 plus
Incidence of H.V.D.	17%	22%	26%	28%
Weight.—				
Pounds	100-150	151-175	176-200	More than 200
Incidence of H.V.D.	14%	22%	24%	36%

One maternal death occurred in the group of grand multiparas, that of an obese, asthmatic patient who was delivered spontaneously, but who then required intrauterine examination for postpartum bleeding. During the general anesthesia for that procedure, the patient became cyanotic and died. The autopsy findings confirmed the clinical diagnosis of death, from anesthesia in a patient with chronic asthmatic bronchitis, emphysema, and pulmonary congestion.

Fetal statistics are compared with those of the general clinic group in Table V. The incidence of stillbirths was almost twice as high among the grand multiparas. There was a significant increase in the incidence of large babies, i.e., those weighing 9 pounds and over. Premature babies occurred slightly less commonly than in the general group.

TABLE V. COMPARATIVE FETAL STATISTICS

	GRAND MULTIPARAS (820 INFANTS 3 POUNDS AND OVER)		GENERAL CLINIC GROUP (10,195 INFANTS 3 POUNDS AND OVER DURING 1951 AND 1952)	
	NO.	%	NO.	%
Term living infants, 5½ to 9 pounds	672	82.0	8,700	85.3
Large living infants, 9 pounds and over	56	6.8	301	3.0
Premature living infants, 3 to 5½ pounds	72	8.8	1,061	10.4
Stillborn fetuses	20	2.4	133	1.3

Comments

Obstetrical complications are increased by grand multiparity. Although maternal mortality in the grand multiparas has been reduced in recent years,[6] it follows that maternal risks must be greater than for the general clinic group. Various authors have shown some differences in the incidence of specific complications. Schram[9] found no increase in the malpresentations in his review of grand multiparas. In contrast Peckham[7] showed that transverse lie was ten times as common in the para x as in the primigravida. In our series all malpresentations taken together were increased twofold when the incidence in grand multiparas was compared with that in the general clinic. Peckham found that

the incidence of placenta previa increased directly with parity. In the present study there was no increase of placenta previa over the clinic incidence. Premature separation of the placenta occurred in 3 per cent of the grand multiparas or more than three times the incidence in the clinic as a whole. This constitutes one of the most serious complications of grand multiparity.

Another serious complication reported among the grand multiparas was rupture of the uterus,[3] although this was encountered only once in our series. Our observations made at the time of vaginal hysterectomy in patients who had borne eight or more viable babies may be relevant. A blunt probe or curette could be passed through the uterine wall with little resistance either at the time of diagnostic curettage or immediately after the uterus was removed. Microscopic sections showed the myometrium largely replaced by hyalinized involuted blood vessels. The myometrium surrounding these vessels contained little elastic tissue.[3] The myometrium of grand multiparas is probably weakened and may be liable to rupture during subsequent pregnancies. The abnormal stress of labor associated with malpresentations such as transverse lie would appear particularly hazardous.

Other complications in these grand multiparas were in keeping with those found in earlier studies.[1, 4, 7, 9] The incidence of twins, prolapsed cord, postpartum hemorrhage, large babies weighing over 9 pounds, and stillbirths was found to be about twice that of the general clinic population. The incidence of primary cesarean section in the grand multiparous patient was increased threefold. Abnormal presentation, cephalopelvic disproportion, and placenta previa were the most common indications for abdominal delivery. Pre-existing hypertensive disease commonly occurs with grand multiparity.[3, 7] Age and obesity as well as parity are probable associated factors in this increased incidence of chronic hypertensive disease.

From this study several therapeutic suggestions concerning the management of grand multiparous patients seem justified:

1. Because of the hazard of malpresentation, vaginal examinations should be done promptly whenever there is any doubt concerning the presenting part. It is desirable to perform these examinations in a delivery room equipped for emergency cesarean section since transverse lie and prolapse of the cord may be encountered.

2. Inadequate progress in labor justifies x-ray pelvimetry. Even with normal pelvic dimensions however, abdominal delivery may be indicated, for excessive-sized fetuses are common in the grand multiparous mothers.[2] Multiparity and especially grand multiparity are no insurance against true cephalopelvic disproportion. Prompt recognition and early abdominal delivery may increase survival of these excessive-sized infants.

3. To prevent postpartum atony and bleeding, it is suggested that an intravenous infusion be started when the patient is taken to the delivery room and that Pitocin be added after delivery of the fetal shoulders and continued for a few hours post partum. It is also suggested that blood be made available for all grand multiparous patients prior to delivery.

4. Diagnostic dilatation and curettage should be performed with extreme gentleness in grand multiparas since the uteri of these patients are easily perforated.

Summary

Eight hundred and twelve cases of grand multiparity from a single clinic have been reviewed. Maternal and fetal hazards have been studied. Some suggestions have been made regarding therapy.

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GAUCHER'S DISEASE COMPLICATING PREGNANCY

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IN 1953 Bromberg, Toaff and Diengott[1] searched the literature for reports of Gaucher's disease complicating pregnancy but failed to find a single case. They reported their own findings in 7 women with this disease who had 13 recorded pregnancies. Also in 1953, Logan[4] reported a case of Gaucher's disease complicated by thrombocytopenia and pregnancy. A careful search of the literature as well as various personal communications has given us no additional information.

Since Gaucher's description of this entity (1882), which he characterized as "idiopathic hypertrophy of the spleen without leukemia," a great deal has been learned of the underlying processes.

The disease occurs predominantly in the Chinese, Japanese, Jewish, and Negro races. Females are affected more often than males. The process is distinguished by the presence of special cells in the spleen, liver, lymph nodes, and bone marrow. In these cells the cytoplasm exhibits a distinct appearance caused by the presence of a special lipid called kerasin.

The most significant clinical sign is progressive enlargement of the spleen, which may reach huge proportions. There are two known forms of this disease. The acute infantile form occurs in the very young and has a rapidly fatal course. Difficulty is encountered in differentiation from Niemann-Pick and Tay-Sachs diseases because of the frequently associated neurological signs and symptoms. The chronic form may start early or at any age thereafter and is compatible with life.

The hereditary nature of Gaucher's disease is still a matter of discussion. Of the known cases recorded in the literature only one third may be regarded as familial. The inheritance is considered to be through a dominant characteristic upon a vertical plane. Several siblings of a specific family may have the disease, yet no recognized involvement may be found in their parents or offspring.

Case Report

A 26-year-old white woman was first seen in July, 1955. She had been married for 5 months. Her menstrual periods had always been regular, beginning at the age of 11, occurring every 28 days, and lasting from 2 to 4 days. The last regular period occurred on May 8, 1955, thus giving an estimated date of confinement of Feb. 15, 1956.

She had been born in Germany, of Jewish parentage, but at the age of 8 had migrated with her family to the United States. At the age of 11 she was admitted to the Mt.

Sinai Hospital in New York City with the diagnosis of Gaucher's disease. At the same time her younger sister was admitted to the hospital with the same ailment. The remaining members of the family underwent a thorough investigation but no further stigmas of the disease were revealed. The younger sister has since married and has produced normally a child who to this date shows no evidence of Gaucher's disease.

Upon initial physical examination the patient was found to be moderately thin but well developed. She had neither myopia nor a malar flush. The heart and lungs showed no abnormalities. Examination of the abdomen showed evidence of a marked enlargement of the spleen. The latter could easily be palpated for 17 cm. below the costal margin, was regular, nontender, and mobile. The liver was just palpable. The pelvic examination confirmed the fact of an early pregnancy.

The laboratory data followed the general picture found in Gaucher's disease. The red blood cell count was 3.92 million with 10.4 Gm. of hemoglobin and a hematocrit of 31 per cent. The white blood cell count was 2,000, with 62 per cent polymorphonuclear leukocytes and 5 per cent monocytes. An x-ray examination of the bones of the lower extremities disclosed flattening of the head of the left femur, believed to be consistent with the clinical diagnosis of Gaucher's disease. The marrow obtained by sternal puncture showed the presence of Gaucher's cells.

The patient's antepartum course was uneventful. She went into labor spontaneously at term and after 12 hours was delivered by low forceps of a live male child weighing 7 pounds, 6 ounces. The immediate postpartum course was also uneventful. On the third day post partum, however, she had an episode of profuse vaginal bleeding. This was readily controlled by transfusion of 500 c.c. of citrated blood. The ensuing course was without incident. Repeated and extensive study of the infant has failed to reveal any evidence of Gaucher's disease.

Comment

In Bromberg's experience, there was little or no interference with the growth of the uterus despite the enormous enlargement of the spleen. This was true in our case. Further study of the records disclosed that hemorrhagic accidents, toxemia, and dystocia were no more prevalent in patients with Gaucher's disease than in others.

It is impossible to reach decisive conclusions on this subject since comparatively few patients have been studied. The occurrence of extensive bleeding during pregnancy forced Logan[4] to perform a therapeutic abortion on his patient. Although the postpartum course was uneventful, a splenectomy was performed in order to produce improvement in the blood picture. Previous observations of patients with Gaucher's disease showed that splenectomy offered no help in altering anemia and thrombocytopenia, and did not cause any arrest in the progression of the disease.

Generally speaking, it appears that Gaucher's disease presents no complicating factor to a pregnancy. In turn, it can also be stated that pregnancy causes no deleterious effect upon this disease. It seems plausible that the study of more cases might eventually prove that such enormous enlargement of the spleen could interfere with the growth of the uterus. The presence of severe anemia, leukemia, and thrombocytopenia is certainly conducive to some hemorrhagic accident following the expulsion of the products of conception.

Until more of these cases are studied, analyzed, and reported there can be no conclusive answer to these problems.

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ACUTE PANCREATITIS COMPLICATING PREGNANCY AND THE PUERPERIUM

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ACUTE pancreatitis is an uncommon complication of pregnancy. In a review of the world literature in 1951, Langmade and Edmondson[1] reported 53 cases and added 8 cases which occurred in 34,791 deliveries at the Los Angeles County Hospital; one additional case was added from a review of 40,394 autopsies. Only the cases diagnosed ante partum or within 6 weeks post partum were included. In their 9 cases, the onset of symptoms occurred in each of the three trimesters with equal frequency.

Coffey[2] reported 4 cases in the hospitals affiliated with Georgetown University during a 5 year period. All their cases occurred during the third trimester of pregnancy. Hanlon and Austin[3] reported a case in which the diagnosis of acute pancreatitis was made during the seventh month of gestation. Jacobs[4] recently reported a case in which the diagnosis was made during the first trimester of pregnancy. Parrish and Richardson[5] recently reported a case in the third trimester of pregnancy. Their case was very severe and exhibited classical tetany associated with a serum calcium of 5.2 mg. per cent.

A direct relationship between pregnancy and pancreatitis has not been established. No known physiologic changes of pregnancy have ever been strongly implicated in the etiology of pancreatic disease. The effect of acute pancreatitis on pregnancy has not been clearly shown. The mortality rate when the two conditions are associated has not been observed in large enough numbers to be conclusive. It appears that the lessened mortality rate in recent cases reflects improved diagnosis and management. In the 9 cases reported by Langmade and Edmondson only one was fatal. The survival of Parrish and Richardson's critically ill patient lends support to the contention that pregnancy makes pancreatitis no more lethal.

The outcome for the fetus in pregnancy complicated by acute pancreatitis cannot be predicted on the basis of experience.[1] The survival of several infants, both premature and full term, indicates that pancreatitis in the mother need not be fatal to the fetus. Recently attention to acute pancreatitis occurring during the puerperium has been emphasized and several cases have been reported.[6, 7] In the 53 cases reviewed by Langmade and Edmondson, the frequency of occurrence in the puerperium was emphasized. Thirty-nine of the 53 cases occurred post partum.

The difficulty encountered in the diagnosis of acute pancreatitis in pregnancy undoubtedly accounts in part for its rarity.[8] This difficulty in diagnosis is also apparent in cases of acute pancreatitis not associated with pregnancy.[9]

Acute pancreatitis is usually considered to be a mildly edematous or a necrotic hemorrhagic disease process of the pancreas.[9, 10] The two may be seen together pathologically and are thought to represent different degrees of severity of the same disease. Emphasis has shifted away from cholelithiasis as the antecedent disease in all forms of pancreatitis. Alcoholism, duodenal ulcer, trauma to the pancreas, mumps, or other viral infections are now thought to play an etiological role. Sachar and Probstein[11] pointed out that patients may develop pancreatitis while dying from some other cause.

Serum amylase and urinary diastase levels are not necessarily correlated with the severity of the disease nor with the prognosis.[12] The pancreas with moderate necrosis of the acini or with little hemorrhage may show ducts containing clear secretion; under these circumstances enzymes are produced resulting in high serum amylase levels. An almost completely necrotic pancreas with massive thrombosis of the pancreatic and splenic veins would be incapable of producing an elevated amylase. In severe attacks of acute pancreatitis the serum amylase level could have returned to normal prior to the time that the amylase determination was taken. The liberation of lipase from the diseased pancreas into the abdominal cavity causes digestion of fat with the production of calcium soaps. The resulting depletion of circulating calcium may be marked and severe. Edmondson and associates[12] showed that in 19 of 27 patients with acute pancreatitis the serum calcium level was below 9 mg. per cent at some time between the first and the ninth day of the illness. Calcium levels of below 7 mg. per cent often indicate a poor prognosis and severe necrosis of the gland.

Caution in the interpretation of serum amylase and urinary diastase determinations should be exercised if morphine has been given. Morphine has been shown to cause spasm of the sphincter of Oddi with obstruction of the pancreatic drainage.[13] To a lesser extent other analgesics are thought to have a similar action.

Because of the rarity of acute pancreatitis in association with pregnancy and the complicated differential diagnosis, special attention must be given to the important factors in diagnosis and management. In order to focus on these features, the following case is reported.

Case Report

Present Illness.—Mrs. P. O., No. 325562, a 22-year-old, registered white woman, para i, gravida ii, was admitted to the Hospital on Jan. 25, 1955, with a chief complaint of chills, fever, vomiting, and right flank pain of 2 days' duration. Her last normal menstrual period occurred on April 23, 1954, and the expected date of confinement was Jan. 30, 1955. For 2 days prior to admission she had noted malaise, coryza, and cough. The cough was accompanied by increased urinary frequency with occasional burning and with terminal dysuria; she denied hematuria. For one day prior to admission she had noted severe right flank pain. The paroxysms of coughing were so severe as to culminate often in the vomiting of recently eaten food.

For several months prior to admission she had been drinking alcoholic beverages to the point of frequent intoxication. She had noted epigastric burning associated with these bouts of drinking. She denied hematemesis and intolerance to fatty foods.

She had had a normal full-term spontaneous delivery of an 8 pound living, female infant in June of 1951. Following the delivery her menstrual periods had remained irregular until the onset of the present pregnancy. Her usual weight was 160 pounds. During the early portion of her pregnancy she felt well except for the epigastric distress associated with consumption of alcoholic beverages.

She was first seen in our prenatal clinic on Jan. 5, 1955. Her weight was 176 pounds and blood pressure 106/70. She appeared well and had no unusual complaints. The serologic test for syphilis was negative. Urinalysis showed no albumin and no sugar. The hematocrit was 39 per cent. She was subsequently seen on Jan. 21, 1955, at which time her weight had decreased to 172 pounds as a result of restriction of caloric intake. Urinalysis showed 30 mg. per cent of protein. She was not seen again until her present admission.

Past History.—The patient's general physical condition had always been good. She had had childhood chicken pox, measles, and mumps. She denied rheumatic fever, scarlet fever, pneumonia, and tuberculosis. She denied symptoms referable to the cardiovascular system. Aside from the epigastric distress, as noted in the present illness, there were no symptoms referable to the gastrointestinal system. She had never had jaundice, abnormally colored stools, nor melena.

Family History.—The patient's father died at age 60 of a "stroke." Her mother, aged 60, was living and well. One brother and 4 sisters were living and well. Her first child was living and well.

Physical Examination on Admission.—Her temperature was 102° F., pulse 108, respirations 20 per minute, blood pressure 106/60, weight 174 pounds. She was noted to be a moderately obese, acutely ill young white woman. She was mildly dehydrated. The posterior pharynx was slightly injected. Examination of the chest showed rare inspiratory wheezes, best heard over both lower lung fields. The heart rate and rhythm were regular at 108 per minute. The sounds were normal and no murmurs were heard. Abdominal examination showed no surgical scars. The uterine fundus was enlarged to 32 cm. above the examination showed no surgical scars. The uterine fundus was enlarged to 32 cm. above the symphysis pubis, and a single fetus was palpable in the occiput right transverse position. There was slight tenderness in the mid upper abdomen and there was very pronounced right costovertebral angle tenderness. Bowel tones were present and slightly hyperactive.

Rectal examination disclosed the presenting part to be floating. The cervix was soft, not dilated, and was 50 per cent effaced. Pelvic measurements demonstrated a gynecoid pelvis.

Laboratory Examination on Admission.—The serologic test for syphilis was negative. The patient was Rh positive. The hematocrit was 35 per cent. The leukocyte count was 15,500 (59 per cent polymorphonuclear leukocytes, 20 per cent stab forms, 19 per cent lymphocytes, 2 per cent monocytes). A catheterized specimen of urine was cloudy and amber in color, with pH 6.0; microscopic examination showed 1 red blood cell per high-power field, 50 to 70 white blood cells per high-power field, and many rods. Culture of a urine specimen taken on admission grew coli-aerogenes bacteria sensitive to tetracycline, Chloromycetin, streptomycin, and Gantrisin. The blood urea nitrogen was 17.8 mg. per cent; the plasma carbon dioxide was 12 mM. per liter; sodium 133 mEq. per liter; chloride 99 mEq. per liter; potassium 3.5 mEq. per liter. A chest x-ray was normal.

Course in the Hospital.—On admittance, the diagnosis of acute pyelitis complicating a term intrauterine pregnancy was made. The patient was treated with intravenous tetracycline, 500 mg. per 1,000 c.c. of 5 per cent glucose in water. On the morning following admittance the temperature was 101° F. Analysis of a catheterized urine specimen was repeated and was very little changed.

Even though the patient appeared improved clinically, and the costovertebral angle tenderness had decreased, the vomiting had persisted. Cultures of blood drawn on Jan.

26, 1955, her first full hospital day, grew coli aerogenes bacteria with the same sensitivity to antibiotics noted in the urine culture. An intravenous pyelogram showed no visualization on either side in the 5 and 20 minute films; 1 hour films were not taken. For her first 5 hospital days she remained febrile with frequent vomiting. Because of continued vomiting, on Jan. 31, 1955, chlorpromazine, 25 mg. intramuscularly, was administered for 2 doses at 6 hour intervals. When she exhibited no vomiting on the subsequent day, chlorpromazine was discontinued.

On Feb. 1, 1955, the sixth hospital day, she went into spontaneous active labor and after 2 hours and 30 minutes delivered a 6 pound, 3¾ ounce living male infant with no immediate complications. The blood pressure 1 hour post partum was 105/70. She was returned to the postpartum ward and continued on intravenous fluids with intravenous tetracycline in dosage of 500 mg. every 6 hours.

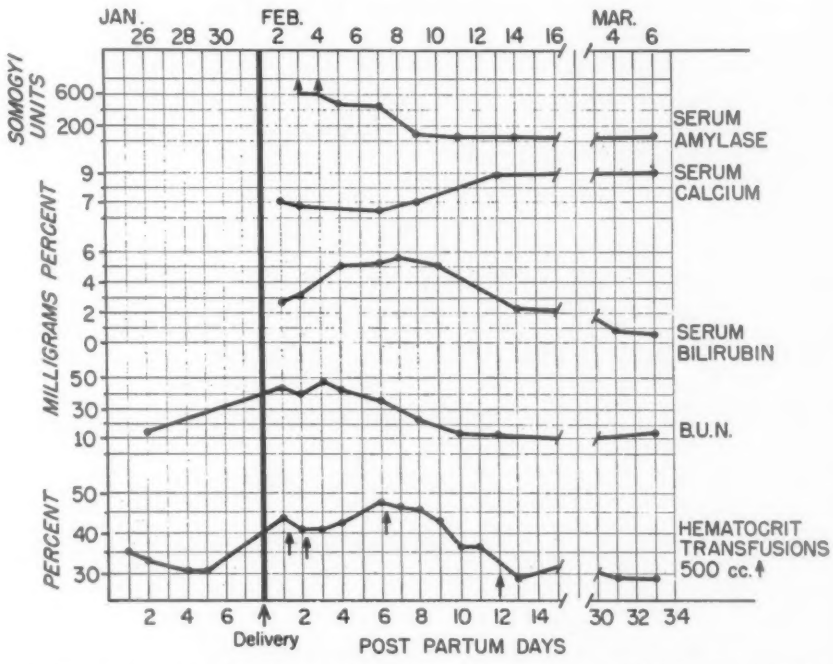

Fig. 1.—Illustrates the laboratory aids in the diagnosis and management of pancreatitis. Note the absence of hematocrit response to whole blood transfusions. From the fourteenth to the thirtieth postpartum day no significant change occurred in laboratory findings.

During the night of the day of delivery and the morning of the first postpartum day, vomiting again became frequent and severe. The vomitus was noted to be guaiac positive, although gross blood was not seen. Her blood pressure slowly dropped to a low of 64/40 on the first postpartum day, with a rise of the pulse to 104 per minute. She became noticeably disoriented with hyperventilation. At this time, the hematocrit was 44 per cent, representing a rise, without transfusion, from the antepartum level of 31.5 per cent. The serum sodium was 140 mEq. per liter; chloride 102; potassium 6.6; and carbon dioxide 10 mM. per liter. The blood urea nitrogen had risen to 44 mg. per cent. The fasting blood sugar was 42 mg. per cent with 5 per cent glucose in water running. The total bilirubin was 2.9 mg. per cent; the icteric index was 15. The postpartum weight of 72.57 kilograms (159.7 pounds) did not change during the first postpartum day.

The immediate treatment of the hypotension and tachycardia was supportive. Continuous 5 per cent glucose in water was administered intravenously. The blood pressure was supported at levels of 90/50 by addition of 20 mg. Neo-synephrine to each 1,000 c.c. of intravenous solution. Tetracycline was also continued intravenously.

On the morning of Feb. 3, 1955, the second postpartum day, the previously noted disorientation was more severe. General neurological examination and examination of the spinal fluid were within normal limits. The guaiac-positive emesis continued and she first complained of marked upper abdominal pain at this time. A clinical diagnosis of pancreatitis was first suspected and a serum amylase determination was obtained and found to be greater than 600 modified Somogyi units (normal King County Hospital up to 150 units). The serum calcium was 6.9 mg. per cent. Total bilirubin 3.3 mg. per cent; icteric index 30. On this day, in addition to supporting the blood pressure with Neo-Synephrine, 500 c.c. of whole blood was given (Fig. 1).

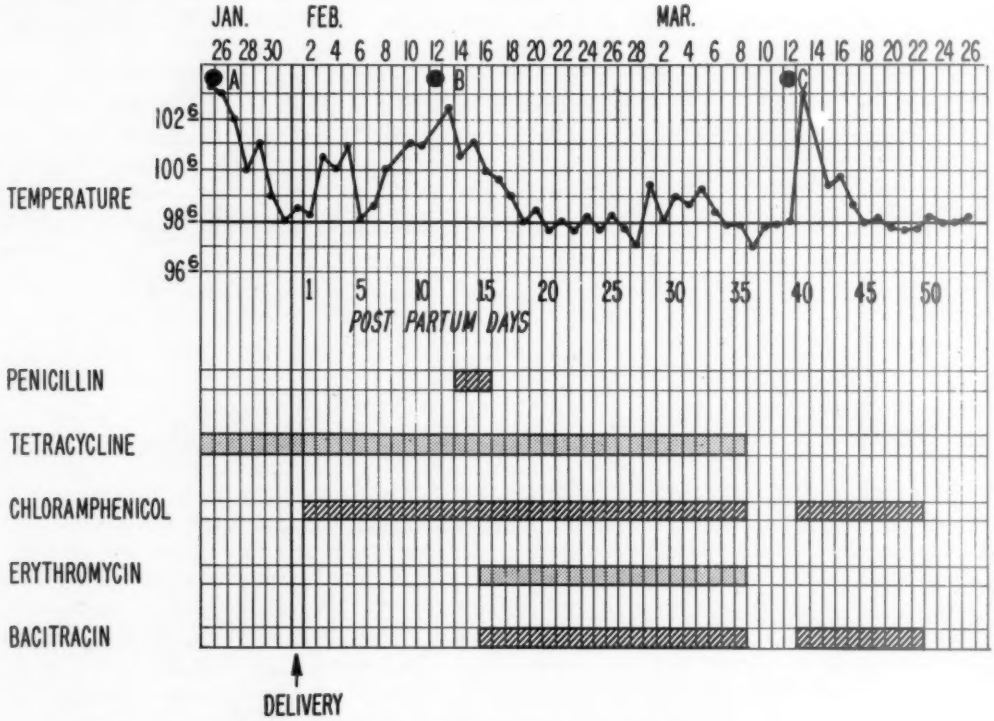

Fig. 2.—Clinical response to therapeutic dosage of the antibiotics. Oral and parenteral routes of administration are not separately noted.

From the third to the sixth postpartum day her condition deteriorated. Jaundice was progressive and deepening and it was necessary to support the blood pressure with Neo-Synephrine and whole blood. Treatment consisted of gastric suction; intramuscular Probanthine; intravenous calcium gluconate, and careful fluid and electrolyte management. On the sixth postpartum day, the serum amylase had fallen to 442 units; serum calcium was 6.6 mg. per cent. Because of the markedly depressed serum calcium and her failure to respond clinically, it was felt that her prognosis was poor.

The clinical course from the sixth to the fourteenth postpartum day changed very little. She remained deeply jaundiced and with a septic temperature curve. The serum amylase fell to 41 units on the tenth postpartum day and the serum calcium rose to 7.1 mg. per cent. On the eleventh postpartum day a blood culture was obtained that grew staphylococcus sensitive to bacitracin and erythromycin, but insensitive to other antibiotics. On the thirteenth postpartum day she was started on a combination of bacitracin,

Chloromycetin, erythromycin, and tetracycline (Fig. 2). From the fifteenth postpartum day the clinical course reflected slow improvement with the return of blood chemistry determinations toward normal. The combined antibiotic therapy was continued until the thirty-fifth postpartum day. During this period she was returned to oral intake of fluids and food and gradual ambulation. A resistant anemia was treated with oral iron therapy.

Her further hospital course was one of slow recuperation with antibiotic therapy for a subcutaneous abscess in the right buttock, and antibiotic therapy for persistent urinary tract infection (Fig. 2). Repeat intravenous pyelograms were normal. An upper gastrointestinal x-ray series and a cholecystogram were normal. She was discharged home on the sixty-fourth postpartum day. The infant had made normal progress and had left the hospital on the seventh day of life.

Subsequent Course.—After discharge from the hospital the patient continued to feel well. She was seen in the postpartum obstetrics clinic on May 11, 1955, at which time physical examination was within normal limits. She has undergone a subsequent normal pregnancy and on May 25, 1956, was spontaneously delivered of a living, 8 pound, 14 ounce normal male infant. Her postpartum course was normal. When last seen on July 14, 1956, she was feeling well and denied symptoms referable to the gastrointestinal tract. General examination and pelvic examination were normal.

Comment

This patient presented an illness of late pregnancy and the puerperium which was severe, complicated, and confusing in its symptomatology, physical findings, and clinical course. Along with the case reported by Parrish[5] and the 2 cases reported by Edmondson,[12] this case represents an exception to the rule that serum calcium below 7 mg. per cent carries a fatal prognosis.[14] This case also points out the difficulty in establishing a clinical diagnosis of acute pancreatitis and the confusion regarding an etiological relationship of pancreatitis to antecedent pathology.[9, 10, 11] The coli-aerogenes urinary tract infection and the coli-aerogenes septicemia are consistent with the belief that pancreatitis can in some instances be caused by blood-borne bacteria, probably arising from the urinary tract.[15] Acute pancreatitis as a complication of acute pyelonephritis has not been previously reported. The association between biliary tract disease and pancreatitis has been studied exhaustively, with the conclusion that the outflowings of bile and pancreatic juices are so closely related anatomically and physiologically that one can scarcely be involved in the disease without the other.[15, 16] For many years the association of coliform urinary tract infections with septicemia and subsequent jaundice has been known.[17]

The severe and persistent antepartum vomiting, shown by our patient, was thought to be due to renal infection and septicemia, but in retrospect could likely have represented the initial attacks of acute pancreatitis. That the patient improved during the antepartum course only to have a severe postpartum exacerbation is consistent with the experience of others.[1, 3] When her clinical course had progressed to the point of disorientation and shock, the diagnosis of acute pancreatitis was first suspected and the initial serum amylase determination was obtained.

The serum calcium level of 6.6 mg. per cent would indicate that the pancreatitis was severe.[5, 12] The transient rise in the blood urea nitrogen exhibited by our patient illustrates the marked urinary nitrogen loss in pancreatitis due to rapid tissue breakdown. The elevated serum potassium bears out the usual finding that in severe cases of pancreatitis the potassium is elevated as a result of tissue breakdown, while in mild cases of pancreatitis the calcium may be low.[12]

An interesting clinical feature of severe necrotizing pancreatitis is shock. Our patient exhibited this clearly, when on the first postpartum day the blood pressure fell from 110/80 to 64/40, while the hematocrit rose from 32 to 44 per cent. The shock responded to whole blood and to vasopressors. In spite of whole blood transfusions in the amount of 1,500 c.c., the hematocrit fell from 44 to 29 per cent over the 12 day period of her most pronounced illness (Fig. 1). Whole blood is also the most available and most physiologic agent in the treatment of the pronounced nitrogen loss that accompanies acute, severe pancreatitis.

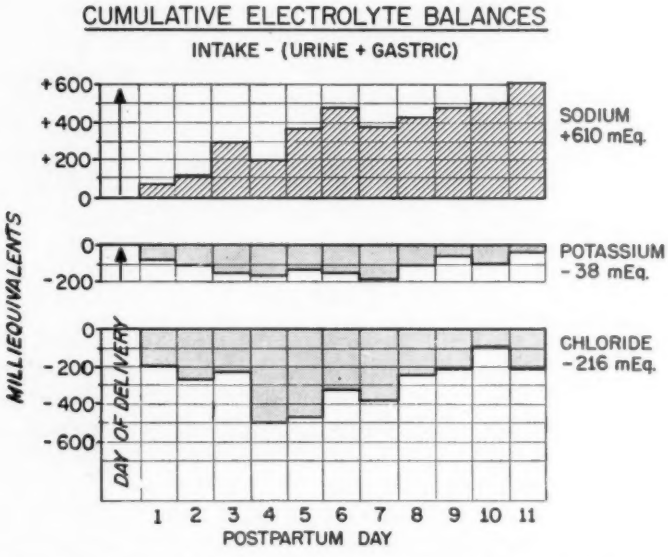

Fig. 3.—Accurate analysis of urine and gastric electrolytes was not begun until the first postpartum day. The cumulative positive sodium balance likely resulted from an unrecognized negative sodium balance at the time of delivery.

There is general agreement concerning the conservative management of acute pancreatitis.[2, 5, 10, 12] The general objectives in treatment are: inhibition of pancreatic secretion, relief of pain, re-establishment of fluid and electrolyte equilibrium, treatment of shock, prevention and control of suppurative complications, and conservative surgical intervention for the drainage of pancreatic cysts or pseudocysts. The need for protein replacement due to the large nitrogen loss in the urine is recognized. Inhibition of pancreatic secretion can best be obtained by decreasing the flow of gastric contents into the duodenum. This can also be partially obtained by giving intravenous glucose solutions in concentrations of less than 5 per cent.[1] A vagal nerve depressant, such as methantheline (Banthine) is given. Sedation is also helpful. Relief of pain can best be obtained with analgesics other than morphine, so as to minimize the chance of drug-induced spasm of the sphincter of Oddi. Careful maintenance of fluid and electrolyte equilibrium is essential (Fig. 3). As illustrated by the fluid balance data in our case, weighing on a special bedside scale is invaluable in recognizing cumulative errors that occur in fluid balance (Fig. 4). The electrocardiogram has proved useful as an adjunct to maintenance of electrolyte balance. The treatment of shock can best be accomplished by the judicious use of whole blood. Intravenous Neo-Synephrine is a valuable aid in some cases. Specific antibiotic therapy in the management of suppurative complications is imperative.

As acute, severe, often fatal recurrences of acute pancreatitis are prone to occur, it appears that the obstetrician is charged with making the diagnosis at the earliest opportunity and with assuming the clinical responsibility for specific treatment. While mild nausea and vomiting are common in early pregnancy, they do not occur in late pregnancy without cause. We feel that awareness of acute pancreatitis as a complication of pregnancy and the puerperium should increase the frequency with which the diagnosis is made so that proper treatment may be undertaken.

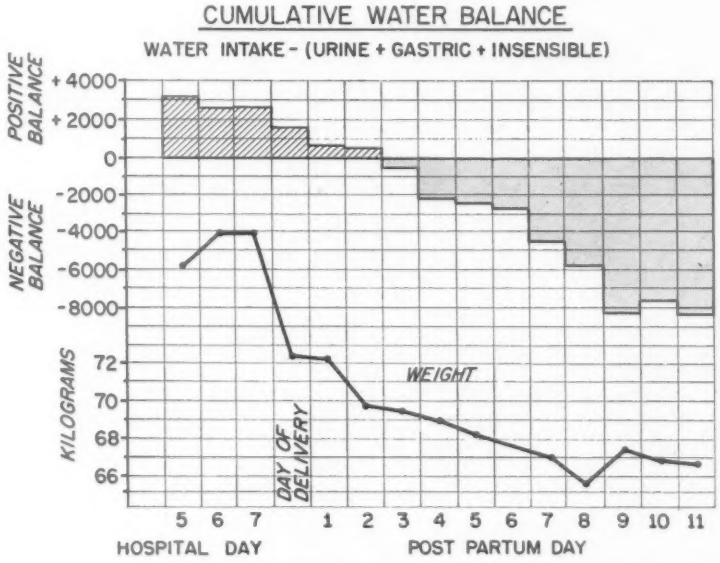

Fig. 4.—The cumulative water balance is shown in milliliters. Any cumulative error in water balance may be largely due to clinical estimation of insensible water loss. Note that frequent weight determinations with the use of a specially designed scale aid in the recognition of the cumulative water balance error. If the clinical estimates of insensible loss had been correct, the weight would have decreased by 8 kilograms from the third to the eleventh postpartum day.

Conclusions

1. Acute pancreatitis occurs in all trimesters of pregnancy and should be suspected in all cases of vomiting of pregnancy.

2. The diagnosis of acute pancreatitis should be considered during pregnancy in the presence of acute abdominal pain, protracted vomiting, circulatory collapse, and electrolyte inbalances.

3. The diagnosis is confirmed by the laboratory finding of elevated serum amylase (levels above 200 Somogyi units) and elevated urinary diastase.

4. Serum calcium is of immediate importance in management and prognosis.

5. Treatment is of the acute pancreatitis, rather than of the pregnancy, and is medical: (a) Nothing per os until the acute phase has subsided; (b) continuous gastric suction by nasal tube; (c) vagus nerve depressant; (d) support of circulatory collapse with whole blood; (e) sedation; (f) careful maintenance of fluid and electrolyte balance; (g) calcium as indicated for depressed calcium levels; (h) surgical intervention for drainage of pancreatic cysts or pseudocysts; (i) protein replacement for large urinary losses of nitrogen.

6. No causative relationship between pregnancy and pancreatitis has been demonstrated.

7. The mortality rate should not exceed that of pancreatitis not associated with pregnancy.

8. When pancreatitis complicates pregnancy, the obstetrician is charged with its early diagnosis and specific treatment.

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THE ETIOLOGY OF DIVERTICULUM OF THE UTERUS IN PREGNANCY

With Report of a Case

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DIVERTICULUM of the uterus in pregnancy is rare. The author has found only 21 cases in the literature.[1-14] It is difficult to know which cases are valid because criteria are not well established and some cases are incompletely described. There is confusion between diverticulum and Rudolph's[11] "ballooning out" phenomenon. According to Schickeles'[1] criteria, the diverticulum must be covered with peritoneum, contain smooth muscle in its wall, contain endometrial glands in its wall, be connected by a tract with the uterine cavity, and be lined with decidua. Rubovitz[10] stated that it must be an ovoid structure, 1 to 2 mm. thick, and have a small aperture connecting with the uterine corpus. Hess[4] emphasized the differential diagnosis from uterus bicornis and didelphys. He stated that the sac is a diverticulum if it is contiguous with the myometrium, has an opening into the uterine cavity, and has no tube or round ligament arising from its lateral margins. All cases reported, except mine, had either fetus or placenta within the diverticulum.

In several earlier cases, the sac was densely adherent to surrounding structures, including the abdominal wall. Many of the patients were multiparas who had had no difficulty in previous pregnancies. Most earlier cases were fatal, because of rupture of the uterus, postpartum hemorrhage, or infection after intrauterine death.

Mrs. G. H., aged 21 years, had her first child in 1953, followed by an abortion in July, 1954. She was first seen on Nov. 15, 1954, with the chief complaint of irregular heavy bleeding since the abortion, rather severe lower abdominal pain throughout her periods, painful bowel movements during her menstrual periods, and intermittent pain in the right lower quadrant. These had all been present for about a year. In August, 1954, she had had an appendectomy (elsewhere), but the pain in the right lower quadrant was unimproved.

Physical examination showed a thin asthenic white woman whose general physical examination was essentially normal. Pelvic examination disclosed the uterus to be in third-degree retroversion and fixed. There was nodular thickening in the cul-de-sac. The uterus was very tender. The left ovary was twice normal size, cystic, prolapsed, and tender. Rectal examination confirmed the pelvic findings. Sigmoidoscopic examination was negative. A pessary was not tolerated. Knee-chest position and hot douches gave no relief. Several courses of premenstrual testosterone and two courses of massive estrogen therapy gave no relief.

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On March 3, 1955, the patient was operated upon. A large, firm, fibrous uterus with mottled whitish areas was noted, in third-degree retroversion. It was adherent to the right cul-de-sac in a very small area. The adhesions were separated and a small piece of tissue from the periphery was pathologically examined. The adherent area of the corpus was on the right posterior aspect. Because of the possibility of endometriosis, a Baldy-Webster uterine suspension was performed. The clinical diagnosis was adenomyosis and endometriosis.

Postoperatively, the patient had rectal pressure during periods, with fullness and pain in the cul-de-sac. The uterus was anteverted. Premenstrual testosterone relieved the patient's symptoms.

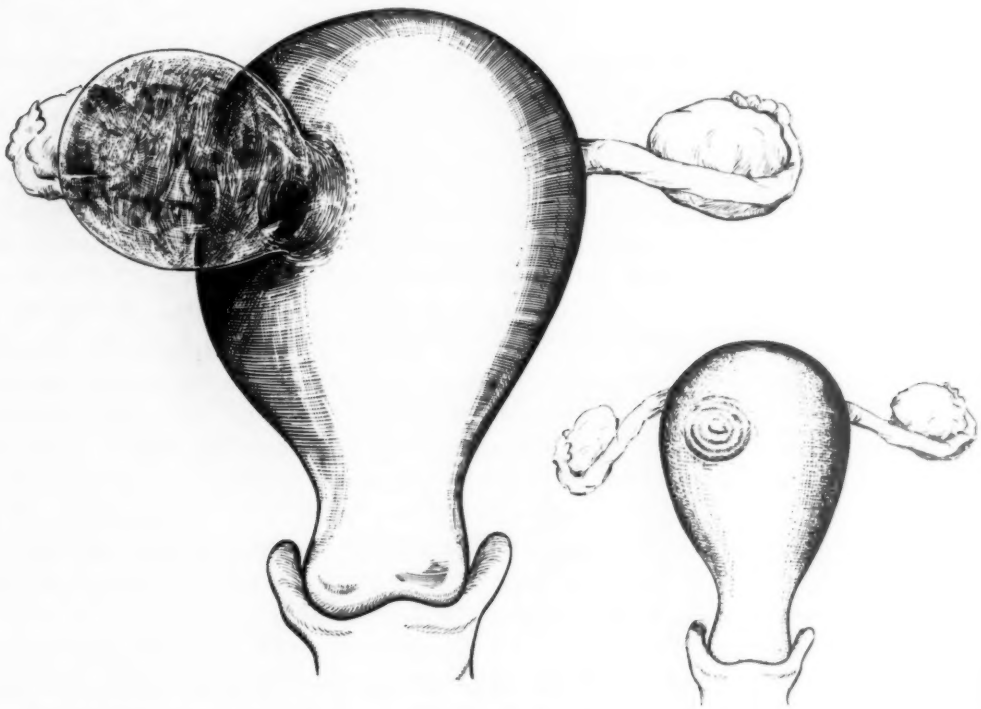

Fig. 1.—The large figure on the left shows the uterus in semidiagrammatic presentation as it appeared at the time of operation. The smaller figure on the right shows the uterus as it appeared after the diverticulum had been reduced manually.

She then became pregnant, the last menstrual period being May 1, 1955. The pregnancy was uneventful until July 12, when she complained of a dull aching pain in the right lower quadrant. At this time, the uterus was three times normal size. Nothing else abnormal was noted on the pelvic examination. On Aug. 2, 1955, the patient complained of a feeling of pressure and swelling in the right lower quadrant. Examination showed the uterus to be the size of a 3 months' pregnancy. There was a tender cystic mass in the right adnexa measuring 2 by 2 inches. The examiner stated that it was probably attached to the uterus.

On August 25, she complained of severe right lower quadrant pain; the mass had increased in size and was exceedingly tender to palpation. The uterus itself was not tender. The diagnosis at this time was hemorrhagic corpus luteum of pregnancy, ovarian cyst, or broad ligament cyst. Analgesics were administered. On September 19, she complained of very severe pain. The right adnexal mass was the size of a 4 months' pregnancy, as was the uterus. The uterus was not tender. The mass was very tender. The patient felt life on the left side only. The impression, at that time, was that the mass was separate and was probably an ovarian cyst with incomplete torsion. She was seen by another obstetrician whose diagnosis was the same. Operation was recommended.

On September 30, the patient was operated upon and a diverticulum of the uterus approximately the size of a 3 months' pregnancy was found. It had a narrow neck measuring 1 inch. It was filled with translucent fluid. It arose approximately 1 inch anterior to and below the insertion of the right round ligament. Kneading the diverticulum caused a partial reduction and the muscle of the wall of the sac could be felt contracting beneath the hand. Further kneading completed the reduction. A defect in the muscle of the uterus, measuring 1 inch, through which the finger could be inserted, remained.

During a contraction, the defect measured approximately ½ inch and never closed completely. The sac re-formed if the uterus was left alone, and filled rapidly if any pressure was exerted on the uterus. By sharp and blunt dissection, incision was carried to the level of the decidua. The wall of the sac was trimmed off. During the procedure, the decidua was inadvertently entered. No amniotic sac was noted. The defect in the uterus was closed by interrupted catgut sutures in four layers.

Preoperatively, the patient had been placed on progesterone, which was continued postoperatively. She had an abortion uneventfully 36 hours later. Pathologically, the wall of the diverticulum contained connective tissue with congestion of the capillaries and smooth-muscle fibers. There was no inflammation, placental tissue, or endometrial glands. The pregnancy was a normal 4 months' gestation.

Comment

This case was different from all other cases found in the literature in that there was no fetus or placenta in the sac. The uterus had been seen at the previous operation, at which time it had no defect. Jarvis[5] has reported a case with a diverticulum during pregnancy which he followed post partum with hysterograms. He noted that the diverticulum gradually disappeared. My patient, like most others, was a multipara. The diverticulum could be reduced.

Summary

Most of the criteria or definitions pertaining to diverticulum of the uterus in pregnancy have been anatomical. The etiology is actually unknown.

Listed below are some possible causes of diverticulum:

1. Improper Müllerian fusion, a muscle defect in the midline. Shaw[12] reported a case of a midline groove post partum which had been the site of a diverticulum during pregnancy. Other diverticula have been reported, including my own case, which did not arise in the midline and which did not contain tube or round ligament in the lateral margins.

2. Ballooning out—uncoordinated contractions and relaxations of uterine muscle. My case seems to meet all the criteria for a diverticulum, yet demonstrates a deficiency in coordination of contraction since stimulation of the sac caused contraction and reduction.

3. Surgical trauma. Although surgical trauma could be a cause in some cases, there have been cases reported without previous surgery.

4. Placental invasion. In my case and Shaw's there was no placenta in the wall.

5. True diverticulum—anatomical. Cases have been reported in which the diverticulum either disappeared post partum or the uterus had been viewed directly in a multigravida and no diverticulum had been seen, only to have a diverticulum develop in a subsequent pregnancy.

Probably none of these factors is causative in all cases of diverticulum.

Other possible causes are discrete weakening of the uterine musculature due to adenomyosis or incomplete rupture during a previous pregnancy.

Any single etiology of diverticulum must answer all objections. If a single cause must be given for all diverticulae, then the "ballooning out" phenomenon of Rudolph is the only one which could explain all the vagaries and objections mentioned above. The other possibility, which is probably correct, is that diverticulum is a mechanical or anatomical abnormality which is due to any of several causes.

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ACUTE LEUKEMIA AND PREGNANCY

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SATISFACTORY data on the incidence of acute leukemia in the general population are unattainable. Southam,[10] however, reports that, during 1947 and 1948, acute leukemia accounted for 4.5 per cent of all admissions to the Memorial Center for Cancer and Allied Diseases, New York City. No significant differences were found in percentages according to race, nationality, or blood type. The occurrence of leukemia during pregnancy is rare, as is conception in leukemic women, the literature having been reviewed by several authors. In 1955, Newson[9] and, during the same year, Gillim[6] reported cases, bringing the total number of recorded cases of acute leukemia in pregnancy to 46. The following case is added.

Report of a Case

A 33-year-old, Spanish-American housewife was referred, on Jan. 14, 1957, to the Bernalillo County-Indian Hospital with the diagnosis of pregnancy complicated by leukemia. The patient, gravida viii, para vii, stated that she was 3 months pregnant but did not know the date of her last menstrual period. She gave the following history: Approximately 4 months prior to this visit, she began to feel "run down." One month later, she was seized with sudden pain in the left jaw followed by nosebleed, for which she failed to seek medical attention. In December, a "shot" which she received from a private physician caused bleeding and ecchymosis. At this time she also noticed ecchymotic areas over the entire body. Intermittent nose and gum bleeding ensued. The past and family histories were irrelevant.

The physical examination showed an obese white woman with no obvious signs of illness. The mucosa of the nose was hyperemic and edematous. The gums showed evidence of recent hemorrhage and the tonsils were hypertrophic. Palpation of the anterior cervical nodes elicited bilateral tenderness. Chest sounds were normal but physiologic murmurs were audible in the heart. The liver was enlarged 2 cm. below the right costal margin. Neither spleen nor kidneys were felt. The fundus of the uterus rose 16 cm. above the symphysis pubis. Vaginal and rectal examinations were normal. The complete blood count was as follows: hemoglobin 10.1 Gm. or 65 per cent; hematocrit 37 per cent; platelets 124,000; white blood cells 23,500, with 66 per cent blast cells. A bone marrow study showed a hypercellular marrow with an increased monocyte: erythrocyte ratio and the megakaryocytes absent. The normal marrow elements were completely replaced by sheets of monotonous mononuclear cells, most of which had one to three nucleoli. Numerous mitotic figures were visible. Occasional cells showed Auer bodies, which are typical of monocytic leukemia.

On March 7, the patient was again admitted to the hospital, after having continued intermittent bleeding from the nose and mouth. Cephalin flocculation was 4 plus; the white blood cells numbered 46,500; the hemoglobin was 9.3 Gm. or 56 per cent; the platelet count was 8,000; and 97 per cent blast cells were seen. The physical findings had not changed since her last admission. She received five blood transfusions and was discharged on March 12 on steroid therapy and oral penicillin. On April 18, an incision and drainage were performed for cellulitis of the right thumb.

In addition to medical supervision, the patient was observed in the obstetric clinic. Several periodic blood transfusions were administered during the course of the disease and pregnancy. On May 3, she was admitted to the hospital for profuse vaginal bleeding. Along with blood transfusions, intravenous drip Pitocin was begun. Two hours and 40 minutes after surgical rupture of the membranes, the patient was delivered of a 4 pound, 6 ounce premature female infant. A specimen of cord blood taken at delivery was negative for leukemic processes. A moderate amount of immediate postpartum bleeding was controlled with intravenous Pitocin. Three units of blood in plastic bags was given. On May 10, the patient was discharged from the hospital in satisfactory condition.

Microscopic examination of the placenta showed some leukemic infiltration on the maternal side only. Examination of the postpartum bone marrow showed excessive proliferation of the blast forms, which composed almost the entire cell component of the marrow, except for a few of the other elements, such as erythroblasts and normoblasts, scattered in between these cells. The granulocyte precursors were essentially absent. An occasional immature form was seen, which presented the possibility that stem cells were of granulocytic origin. A diagnosis of acute stem-cell leukemia was made.

Twenty days after delivery, vaginal bleeding occurred. This was controlled with plastic bag blood transfusions and increased steroid therapy. On May 29, new ecchymoses began to appear, with retinal hemorrhage in the macular area. There was a decrease in the white blood cells and an increase in the blood uric acid. Mercaptomerin and extensive cortisone therapy was instituted without significant results. On June 8, following a profuse generalized hemorrhage, the patient died.

Postmortem examination showed the skin to be covered with large purpuric areas. Nearly all the internal organs were hemorrhagic. Microscopic examination showed that every organ, including the endometrium and myometrium of the uterus, was extensively infiltrated with acute stem-cell leukemic processes.

Comment

Stem-cell leukemia, exemplified by the foregoing case, has been designated by various hematologists and pathologists as "unclassified acute leukemia." The 46 reported cases of acute leukemia represent 27 myelogenous, 12 lymphatic, 5 monocytic, and 2 unclassified. The parity and age of the patients, ranging from gravida i to para viii and from 15 to 40 years, were evidently unrelated to the disease. Of the 47 cases of acute leukemia only 2 were diagnosed before the onset of pregnancy, the others being detected between the fourth and seventh months of gestation. The maternal mortality rate was 100 per cent.

It has been stated that the average life expectancy after the appearance of symptoms is 7.67 months.[6] Four patients of the 47 patients referred to died during the pregnancy and 5 during the parturition; the others survived over 14 days. Postpartum hemorrhage was severe in 6 cases but fatal in only one. A case of hemorrhage on the second postpartum day was treated with curettage followed by packing with oxidized gauze. Peritonitis due to perforation of the uterus ensued and the patient died 61 days after delivery.[7]

The causes of death fell into three major categories: (1) overwhelming infection; (2) hemorrhage; and (3) exhaustion. After the advent of systemic antimicrobial drugs, infection was less frequently the immediate cause of death. Few cases terminated in hemorrhage, this complication being adequately treated with transfusions. The most common cause of death was exhaustion. In the absence of any important localized change, the patients became progressively weaker, to a point at which vital processes ceased. Leukocytosis or localized leukemic infiltration was seldom responsible for death.

There is no evidence that the presence of pregnancy enters as an etiological factor, the cause of leukemia still remaining obscure. Marked infiltration of the uterus, tubes, and ovaries has been observed in several autopsied specimens.

In spite of the fact, however, that leukemic cells have appeared on the maternal side of the placenta, leukemic substances have never been found to pass the placental barrier. Ohlsson[2] discovered normal blood cells in the chorionic villi of the placenta in the presence of leukemic cells in the intervillous spaces. Stransky,[2] Bungeler,[2] and Morrison and Samwick[11] testified to the reverse in cases of congenital leukemia but did not find it duplicated in leukemic mothers.

Evidence precludes any theory that pregnancy influences the course of leukemia. When one considers the extent to which leukemia alters the hematologic picture, hemorrhage following vaginal and operative deliveries of these patients is rare. Moreover, the leukemia does not necessarily prevent the patients carrying their pregnancies to term. And, although premature deliveries are frequent, therapeutic abortion is not indicated. Birge and associates[4] recorded a case of acute leukemia with pregnancy, complicated by eclampsia. After delivery of a premature nonviable infant, a spontaneous remission of the leukemic state followed. The mother regained satisfactory health for a period of 21 months, at which time a relapse preceded death.

Leukemia has never been demonstrated in any child born to a mother with the disease. Congenital abnormalities ascribed to these children are rare. From the standpoint, therefore, of both mother and baby, these patients, I feel, should be permitted to carry their pregnancies to term and be delivered in the normal manner.

Conclusions

It is evident from the foregoing case and those reviewed that pregnancy does not essentially alter the course of acute leukemia, fatal uterine hemorrhage being rare. Although leukemia is a definite cause of premature birth of the offspring, a leukemic mother has never been known to give birth to a leukemic child. Interruption of the pregnancy is of no benefit and may hasten the death of the mother.

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Gynecology

CLASSIFICATION AND CLINICAL STAGING OF CARCINOMA OF THE UTERUS

A Proposal for Modification of the Existing International Definitions

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A COMPARISON of statistics is of great value in improving the treatment of malignant tumors. Uniformity in statistics on carcinoma of the uterus requires precise definitions of the varieties of the disease. A classification system must permit each case of primary carcinoma to be exactly and uniformly classified. Most cases can be allotted to the two conventional groups: carcinoma of the cervix and carcinoma of the corpus. There are rare cases, however, in which the origin of the growth clinically cannot be accurately ascertained. While in general agreement with the definitions adopted in 1950 and used by the Collaborators in the *Annual Report,* we would like to recommend the establishment of three additional groups, thus making an exact classification of each case possible. The three groups are: carcinoma vaginae et cervicis, carcinoma uteri et ovarii, and carcinoma pelvis.

Carcinoma Vaginae et Cervicis.—This classification should be used when the cervix cannot be examined at the beginning of the treatment, thus making it impossible for the examiner to determine whether he is dealing with a primary tumor of the vagina or of the cervix.

The number of cases allotted to this group should always be given in the presentation of therapeutic results in carcinoma of the cervix. Also, we must insist as a rule that a carcinoma of the vagina which involves the cervix is statistically regarded as a case of carcinoma of the cervix.

Carcinoma Uteri et Ovarii.—This designation should be used in three instances:

1. When there is a carcinomatous involvement of both the uterus and the ovary at the first examination and it cannot be microscopically stated which tumor is the primary.

2. When a patient previously submitted to oophorectomy because of carcinoma of the ovary and not simultaneously curetted develops a corpus carcinoma within 5 years after the oophorectomy.

3. When a patient radiologically treated because of a corpus carcinoma at the same time has a palpable pelvic tumor extrinsic to the uterus, which later is proved to be a carcinoma of uncertain origin.

Carcinoma Pelvis.—This term is reserved for cases in which the site of the growth is in the pelvis, the uterine mucosa and most of the pelvic organs are involved, and it is impossible to ascertain macroscopically or microscopically the origin of the growth. A squamous-cell carcinoma of this character should, however, be regarded as carcinoma of the cervix.

Classification of Carcinomas of the Cervix

Much of the difficulty in securing comparability of different statistics in respect to relative and absolute cure rates is due to the fact that the samples of patients suffering from cancer and treated at different centers are not of equal clinical quality. At present, division of the total material into stages containing cases of equal anatomical spread is the only method available for obtaining comparability. The stage of the disease is probably the most important factor in the ultimate outcome of a case.

It is obvious that the anatomical spread of the carcinoma cannot be estimated as accurately by clinical examination as by histopathological findings.

We must, however, insist on a clinical staging as the basis of presenting therapeutic statistics in carcinoma of the uterus. Clinical staging will suffice for comparing radiotherapeutic results and for comparing surgical and radiotherapeutic results, provided the rules for staging the disease and for presenting the results are standardized and the recommendations strictly observed. All cases examined should be reported—completely treated, incompletely treated, and not treated. Although the *Annual Report* so far has permitted cases not microscopically examined to be included, we think it would be wise to require a microscopic verification in all cases.

The Clinical Staging.—Clinical staging should be performed by an experienced specialist immediately before the first treatment. If possible the examination should be done under anesthesia. The examination methods to be used in clinical staging are palpation, inspection (including examination by the colposcope and the curette), and x-rays of the lungs and bones. Findings by urography, arterio- or venography, or by other methods should not be taken into consideration as a means of allotting a case to its appropriate stage nor should anything but facts revealed by examination be taken into account. The stage of each case decided at examination prior to treatment should remain unchanged.

In 1950 the International Congress on Obstetrics and Gynecology recommended the following definitions of the different clinical stages:

INTERNATIONAL CLASSIFICATION OF THE STAGES OF CARCINOMA OF THE UTERINE CERVIX

Stage 0 Carcinoma in situ, also known as preinvasive carcinoma, intraepithelial carcinoma, and similar conditions.

Stage I The carcinoma is strictly confined to the cervix.

Stage II The carcinoma extends beyond the cervix but has not reached the pelvic wall. The carcinoma involves the vagina but not the lower third.

Stage III The carcinoma has reached the pelvic wall. (On rectal examination no "cancer-free" space is found between the tumor and the pelvic wall.) The carcinoma involves the lower third of the vagina.

Stage IV The carcinoma involves the bladder or the rectum, or both, or has extended beyond the limits previously described.

The significant reasons for adding Stage 0 to the classification were (1) to call attention to the importance of early diagnosis, (2) to keep preinvasive carcinoma separate from invasive cancer, and (3) to prevent the inclusion of the preinvasive cases in statistics of treatment results.

Acceptance of the International Classification has been of importance in the evaluation of therapeutic results. Experience has, however, shown that a direct comparison of therapeutic results in the different stages is not entirely justifiable because of the variations in the quality of the primary material and because of the inaccuracy inherent in any clinical method of staging cancer. The main sources of inaccuracy in staging carcinoma of the cervix include: (1) precise microscopic differentiation between dysplasia, intraepithelial carcinoma, and early invasive carcinoma; (2) clinical evaluation of the degree of involvement of the parametrium in Stages II and III; and (3) the proper allocation of cases to Stage IV.

We do feel that the number of stages should not be increased but that a subgrouping of the stages is advisable for the purpose of giving more accurate information on the quality of the material. The different stages are discussed below.

Stage 0.—The diagnosis of preinvasive carcinoma is important, but opinions vary as to which cases should be regarded as dysplasia and which as carcinoma in situ. Authors also disagree as to the importance of intraepithelial carcinoma as a premalignant lesion. *Therefore we propose that Stage 0 be omitted from the clinical classification.*

Stage I.—Experience evidently has shown that preclinical invasive carcinoma of the cervix differs from the grossly obvious lesions of Stage I as far as prognosis is concerned. Metastases to pelvic lymph nodes are rare in the very early cases. The percentage of such cases in the Stage I category will influence the over-all results in this stage. This also holds true for large endocervical and ectocervical disk-shaped or cauliflower-like tumors, which sometimes might be difficult to distinguish from Stage II cases. In order to improve upon the comparability of series of these cases *we suggest a subdivision of Stage I into Groups A, B, and C.*

A case should be allotted to *Stage I, A* if the growth is preclinical or less than one centimeter in diameter. A case of questionably invasive carcinoma and a so-called microcarcinoma (Mestwerdt) would belong to this group. Although all have agreed to signify as invasive carcinoma only cases in which the atypical proliferating epithelium has penetrated the basal membrane or broken into blood vessels or lymphatics, experience has shown that it is impossible to come to an agreement on the precise characteristics of early

invasion. There is no doubt that in many cases of questionably invasive carcinoma a careful study of several blocks with serial sections will disclose the actual invasiveness of the atypical epithelium. Therefore, we propose that borderline cases of this type be allotted to Stage I, A. Truly preinvasive lesions will, of course, remain excluded from consideration in any series of carcinoma cases.

A case should be allotted to *Stage I, B* if the growth has a diameter of 1 to 5 cm., and to *Stage I, C* if the diameter exceeds 5 cm. A carcinoma of the cervix with extension to the corpus should also be allotted to Stage I, C.

Stages II and III.—The widest range of difference in interpretation of the rules for staging lies in distinguishing Stage II from Stage III in cases in which the degree of involvement of the parametria is the deciding factor. Regarding Stages II and III as one group is not advisable, for in many series the number of cases allotted to Stages II and III constitutes the majority of the cases treated. In this respect, however, we wish to point out that in forming an opinion on the results achieved in, for instance, Stage II at one institution, the figures for Stage III must also be considered. Therefore, the total series of such cases should be given in all reports on cancer of the cervix.

The present international definitions of Stages II and III are not distinct as far as the extension of the growth into the parametrium is concerned. The deciding factor in allotting a case to Stage II or III should be, as far as the parametrium is concerned, the extension of the tumor in the pelvis. *A swelling on the pelvic wall* should no longer be taken into consideration in the staging, as there is reason to believe that at some institutions it is often used as a criterion for allocating cases to Stage III. The differential diagnosis between an inflammatory process or endometriosis and a carcinomatous mass on the pelvic wall, free from the primary growth, is often clinically so difficult that it is inadvisable to place such a case in Stage III solely on the basis of such a mass.

We suggest that:

1. A carcinoma should be allotted to *Stage II* if it involves the vagina but not the lower third and/or the carcinoma infiltrates the parametrium but has not reached the pelvic wall.
2. A carcinoma should be allotted to *Stage III* if it involves the lower third of the vagina and/or the carcinomatous infiltration has extended into the pelvic wall, when on rectal examination *the infiltration feels firm and nodular,* and there is no smooth "cancer-free" space between the tumor and the pelvic wall.

Experience obviously has shown that the prognosis is entirely different in cases of Stage II with encroachment of the tumor on the vaginal wall and in cases of Stage II with obvious parametrial involvement. *Although we fully realize that a subgrouping of the Stage II cases with regard to the parametrial involvement will be subjective, we suggest that such a subdivision be made, for it will give information regarding the quality of the material.*

Stage IV.—It has surprised us that the requirements for allotting a case to Stage IV seem to vary considerably as far as involvement of the bladder or rectum is concerned. Bullous edema is seen in cases of cystitis or pelvic inflammation. A positive biopsy from the bladder or rectum is desirable to allot a case to Stage IV but it is obvious that we cannot insist upon such a requirement. *We suggest, however, a subdivision of the Stage IV cases dependent upon histological proof of invasion of the bladder or rectum, or the presence of an ulceration or a fistula.* The presence of ridges and furrows in the wall of the bladder should be considered as a clinical sign of involvement only if they remain at digital examination from the vagina or rectum.

Considering the various facts mentioned we recommend that the definitions of the stages of carcinoma of the cervix be modified to read as follows:

RECOMMENDED CLINICAL STAGING IN CARCINOMA OF THE CERVIX

Stage I The carcinoma is strictly confined to the cervix.

Group I, A Preclinical carcinoma or less than 1 cm. in diameter.

Group I, B A carcinoma 1 to 5 cm. in diameter.

Group I, C A carcinoma more than 5 cm. in diameter. The growth has extended to the corpus.

Stage II The carcinoma involves the vagina but not the lower third. The carcinoma infiltrates the parametrium but has not reached the pelvic wall.

Group II, A Carcinoma encroaching upon the vaginal wall, but not obviously infiltrating the parametrium.

Group II, B Carcinoma infiltrating the parametrium.

Stage III The carcinoma involves the lower third of the vagina. The carcinomatous infiltration of the parametrium has extended into the pelvic wall, when on rectal examination the infiltration feels firm and nodular and there is no smooth "cancer-free" space between the tumor and the pelvic wall.

A swelling on the pelvic wall, not attached to the tumor, should not be considered in the staging.

Stage IV The carcinoma involves the bladder or the rectum, or has extended outside the true pelvis, i.e., below the vaginal inlet or above the pelvic brim (distant metastases).

Group IV, A Clinical invasion of the bladder or rectum.

Group IV, B Histologically proved invasion of the bladder or rectum, ulceration, or fistulas. Extension of the carcinoma outside the true pelvis.

Only cases of invasive carcinoma should be included. The staging should be performed prior to the treatment and should not be changed. It is desirable that the staging should be carried out under anesthesia. Findings at urography or venography or at surgery should not influence the staging.

Classification of Carcinomas of the Corpus

Many attempts have been made to find a suitable classification and subgrouping for carcinoma of the corpus. A classification based on the findings at operation, on the examination of the extirpated uterus, and on the metastases present is of value for presenting surgical statistics. It is not useful for clinical purposes, however.

Heyman has proposed a classification and staging that are applicable to all kinds of cases. The disadvantage of the stage grouping recommended is that it considers the operability rate, a factor that many years ago was rejected from the staging of carcinoma of the cervix. Although the staging suggested by Heyman has been adopted by the *Annual Report* it has not gained universal recognition.

Recent studies have shown that metastases to pelvic lymph nodes are more common in cases of corpus carcinoma than has been previously mentioned in literature. This holds true in particular for cases of corpus carcinoma deeply invading the myometrium or/and extending to the cervix. It is important, therefore, to separate cases of carcinoma of the corpus and endocervix from cases of carcinoma of the corpus. As a rule this is possible by a fractional curettage or hysterography. Clinically it is, however, impossible to estimate the degree of carcinomatous infiltration of the myometrium.

Recent observations have emphasized the correlation between the degree of the differentiation of the corpus carcinoma and its behavior, inasmuch as a

highly differentiated carcinoma has a tendency to grow superficially while an anaplastic or solid carcinoma has a propensity for deeply invading the uterine wall. We have seriously discussed this observation as far as subgrouping of the corpus cancer cases is concerned. We feel, however, that clinical staging of corpus carcinoma should not include a microscopic criterion.

We recommend that the definitions of the stages of carcinoma of the corpus be modified to read as follows:

RECOMMENDED CLINICAL STAGING IN CARCINOMA OF THE CORPUS

Stage I The carcinoma is confined to the corpus.

Stage II The carcinoma has involved the corpus and the cervix.

Stage III The carcinoma has extended outside the uterus but not outside the pelvis.

Stage IV The carcinoma has involved the bladder or the rectum, or has extended outside the true pelvis.

Summary

The International Classification in carcinoma of the uterus and the clinical staging in carcinoma of the cervix have been of considerable value in the evaluation of treatment results. Experience has shown, however, that a direct comparison of therapeutic results in the different stages is not justifiable because of the variations in the quality of the primary material and because the staging demands more from the gynecological palpation than can be filled by this examination.

We believe that the definitions of the various stages have to be more accurate and that a subgrouping of the stages will give better information on the quality of the material. We have therefore, suggested a subgrouping of the stages. The number of stages is not increased. Although the diagnosis of preinvasive carcinoma is important, we propose that Stage 0 should be omitted from the clinical classification. As it will still be difficult to distinguish cases of Stage II with parametrial infiltration from cases of Stage III, we wish to point out that in forming an opinion on the results achieved in one of these stages the figures for the other stage also must be considered. A swelling on the pelvic wall free from the primary growth should not permit a case to be allotted to Stage III. A microscopic verification should be required in all cases.

SIMULTANEOUS COLPOSCOPY AND CYTOLOGY USED IN SCREENING FOR CARCINOMA OF THE CERVIX

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THE purpose of all the available screening methods used in the diagnosis of carcinoma of the cervix is the detection of the early stages of the disease which otherwise escape recognition by the simple methods of clinical examination, such as palpation, visualization, Chrobak's silver probe test, etc. These stages are usually asymptomatic, corresponding histologically to intraepithelial or early invasive carcinoma and are therefore referred to in this paper as "preclinical carcinoma."[19]

The accuracy of cytology, when used as a screening procedure in the detection of preclinical carcinoma of the cervix, is usually quoted in the literature as between 70 and 90 per cent. Achenbach, Johnstone, and Hertig[1] gave 70 per cent; Cuyler, Kaufmann, Palumbo, and Parker,[6] 89.4 per cent; Limburg,[16] 89.3 per cent; Graham,[11] 86 per cent; and this study 88.5 per cent. Of course the degree of accuracy depends largely on various factors, namely, the number of control smears taken, the technical quality of the smear, the experience of the cytologist, etc.

The first single screening cytological examination, however, leaves a not inconsiderable percentage of undetected cases of preclinical carcinoma. If one considers the tremendous value of early diagnosis in the results of therapy, it becomes imperative that a way must be found to improve our diagnostic accuracy without resorting to multiple re-examinations.

Screening Methods

Undoubtedly, an error of method can best be corrected through the use of a second, independent technique. If only one method is used, certain misdiagnosed cases will necessarily remain undetected. It would be possible to correct a cytological error to a certain degree by a parallel clinical examination with the frequent use of biopsy taken from "suspicious" areas, if present. These areas, however, viewed with the naked eye, are usually not very specific for carcinoma, presenting themselves as white spots (leukoplakia) or as red areas (erythroplakia†). This method entails the problems of proper selection of the cases for biopsy and of the choice of the exact spot on the cervix from

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†We consider this term as more appropriate in designating the gross feature of reddening, usually referred to as "erosion."

which the biopsy is to be taken. The nonspecificity of the "suspicious" areas already mentioned usually results in a very large number of unnecessary biopsies.

Fremont-Smith, Graham, and Meigs[9] for example, showed that, in 30 cases of intraepithelial carcinoma, the original biopsy was positive in only 40 per cent. In another series of 40 cases of Graham and Meigs,[12] the original biopsy resulted in 70 per cent correct diagnoses. Foote and Stewart[8] showed that routine biopsy at 6 and 12 o'clock showed only 74 per cent accurate diagnoses. Ross[23] stated that, in 44 cases of intraepithelial carcinoma of the cervix, a suspicion was raised during clinical examination in only 4 cases. Moreover, 11 of these cases were reported as cytologically negative.

Similarly Hartford[13] reported upon a series of 7,382 cytologically examined women; in only 32 of 45 cytologically positive but clinically unsuspected cases was the first biopsy positive for carcinoma; in the remaining 13 patients only a later biopsy led to the same diagnosis.

Difficulties of this type have finally led to the "four-point biopsy" as described by Foote and Stewart,[8] as well as to the more extensive method of coning biopsy according to Ayre.[2]

The efficiency of biopsy control short of the coning procedure in cytologically falsely negative cases seems doubtful, however, for it is entirely possible to obtain a falsely negative biopsy as well in a cytologically falsely negative case, and thus miss the case.

The difficulty of clinical selection of cases in which a biopsy is indicated in spite of negative cytological results can be met to a certain extent by the iodine test of Schiller. This test can indeed reduce the number of necessary biopsies, especially if the clinician has experience in the accurate interpretation of iodine-negative areas.

Daro, Rubenstein, and Gollin[7] reported on a combination of cytology and multiple punch biopsy after the Lugol test in 500 patients. The accuracy of the cytological diagnosis was 95.4 per cent, and of the biopsy 90.7 per cent, while both methods together resulted in 98.3 per cent accuracy of detection in this series of carcinomas, as far as an objective statement is possible. There remains, however, still the question as to whether other cases have escaped this combination of cytological diagnosis with a largely nonspecific method.

Advantages of Colposcopy Used With Cytology

The control of errors of a specific method can be achieved ideally only through the use of another equally specific screening method. Such a method is the colposcopy of Hinselmann.[14] The almost ideal supplementation of colposcopy with cytological diagnosis appears in the following series of facts:

1. The simultaneous use of colposcopy results in no significant loss of time, because it merely replaces the necessary speculum examination.

2. The colposcopic diagnosis is immediate and arrives at its results merely through examination of the patients.

3. The exact spot at which a biopsy need be made can be chosen with great accuracy by use of the colposcope. It is possible to reduce greatly the number of necessary biopsies.

4. With negative cytology, colposcopy can dispose of suspicion on the basis of clinical examination in a great number of cases and thus reduce further the number of necessary control biopsies.

5. Colposcopy enables one to perform a target smear for cytological study according to the method of Ayre.[2]

The importance of the combination of both methods seems to us to lie in their fundamentally different approach in arriving at the same goal. Therefore it can be expected with great probability that by the parallel use of both methods an error will not occur simultaneously in both methods in any single case.

The main disadvantage of colposcopy is the fact that early carcinomatous changes of the endocervix will as a rule escape detection by this method. Thus this field remains entirely in the realm of cytological diagnosis. As regards changes in the area of the ectocervix, however, the results of colposcopy can at least be equated with those of cytology.

Results

Our colposcopic results for the years from 1949 through 1954 have been previously reported.[19] The results for the years from 1954 through 1956 appear in Table I.

TABLE I. RESULTS OF COLPOSCOPY IN THE DIAGNOSIS OF PRECLINICAL CARCINOMA OF THE ECTOCERVIX (1954 THROUGH 1956)

Number of patients examined		18,112
Total number of preclinical carcinomas of the cervix discovered	306	
Number of preclinical carcinomas of the ectocervix	275	
Number of colposcopically discovered preclinical carcinomas of the ectocervix	251	91.3%

The results of cytology in the same clinic population computed from the first smear only was 88.5 per cent, as appears in Table II. Since the first smear was inadequate in 5 preclinical carcinomas and was not repeated because the cases were already diagnosed colposcopically, the actual accuracy of cytological diagnosis can be said to have been 90.1 per cent when these 5 cases are left out. This percentage must be interpreted with regard to the fact that patients are simultaneously subjected to two different methods of screening examination, serving as controls for each other. If only cytology had been used some of the cytologically negative cases could be missed entirely. The resulting apparent accuracy of cytology alone would then be higher.

TABLE II. RESULTS OF DIAGNOSIS OF 306 CASES OF PRECLINICAL CARCINOMA OF THE CERVIX WITH SIMULTANEOUS USE OF CYTOLOGY* AND COLPOSCOPY

	NO.	%
Cytologically positive Colposcopically positive	220	71.9
Cytologically negative Colposcopically positive	26	8.5
Cytologically inadequate Colposcopically positive	5	1.6
Cytologically positive Colposcopically negative	51	16.6
Cytologically negative Colposcopically negative	4	1.3
Total number of cases diagnosed through the use of both methods	302	98.7

*As evaluated from the initial smear only.

It has seemed most efficient to use both methods routinely during the examination of each patient, regardless of the clinical and macroscopic impressions and findings. At the University Frauenklinik, Graz, this is done in such a way that the colposcopist takes the smear subsequent to colposcopy and also performs biopsies in colposcopically suspect cases without waiting for the cytological diagnosis. Only thus is it possible to compensate for any cytological

error. In colposcopically unsuspected cases which turn out to have suspicious cytological findings, the colposcopy is repeated and, if the findings persist as negative, a curettage of the cervical canal is performed at this time by the

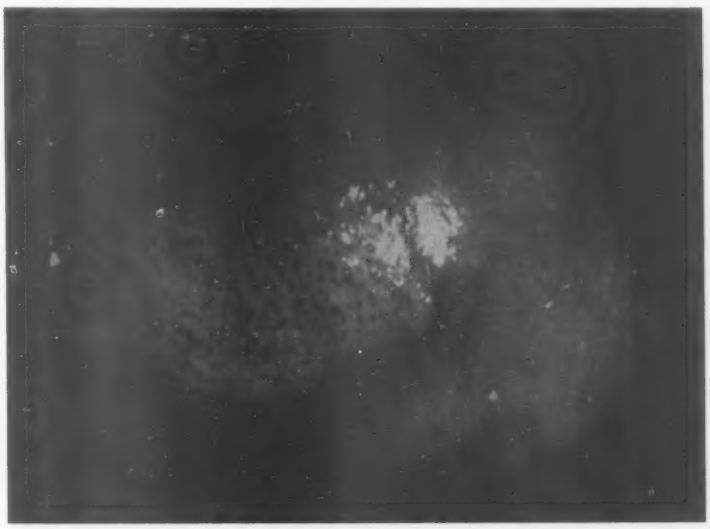

Fig. 1.—Area of elevated ground ("Grund") leukoplakia. Biopsy showed intraepithelial carcinoma.

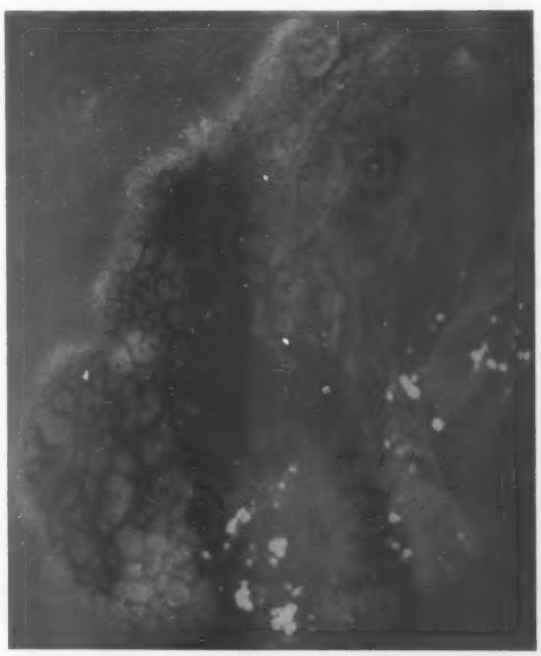

Fig. 2.—Area of rough mosaic ("Felderung") and ground ("Grund") leukoplakia. Biopsy showed intraepithelial carcinoma.

colposcopist. The results of detection of preclinical carcinoma under this system appear in Table II. If only cytological methods had been used during this time, at least 30 cases of preclinical carcinoma would have been missed at

the first examination. With colposcopy alone, on the other hand, 55 cases of preclinical carcinoma would have gone undetected. Of the 55 carcinomas, however, 31, or 10 per cent of all the cases, were purely intracervical in location.

With the simultaneous use of both methods we undoubtedly have great accuracy in the diagnosis of preclinical carcinoma of the cervix. This has also been recognized by a number of other authors.[3, 10, 16, 21, 26]

Comment

It is not the purpose of this paper to enter into the details of colposcopic diagnosis. This has been adequately covered in the very voluminous literature concerned with this topic.[10,14, 15, 18-20,27]

In the more recent American literature it has been discussed in particular by Lang,[15] Navratil,[19] Schmitt,[27] and Scheffey.[24, 25, 26] We do wish, however, to re-emphasize the simplicity of colposcopy, and the possibility it offers of obtaining greater accuracy in the use of target punch biopsies. In addition, one may point out the usefulness of colposcopy in providing a direct method of observing the various physiological and pathological changes of the cervix. It is easily understandable that a magnification of 10 to 20 times can better demonstrate the morphological changes associated with or preceding the development of carcinoma of the cervix than can the naked eye. One can arrive at this conclusion only after considering the multiplicity of pictures which results under the colposcope from the macroscopically uniform picture of an "erosion." Figs. 1 and 2 show two of the various aspects which an intraepithelial carcinoma may display through the colposcope. Follow-up of pathological lesions through the use of photocolposcopy is an additional valuable method in tracing the morphological evolution of various disease processes of the cervix.

Summary

Colposcopy is particularly useful as a specific method of early diagnosis of preclinical carcinoma of the cervix, when used in conjunction with cytology. Thus used, it compensates greatly for any error of cytology. This fact is demonstrated by the results of routine examinations of 18,112 patients in whom 306 preclinical carcinomas were discovered.

A second advantage of colposcopy is the ability to aim a punch biopsy with great accuracy and to avoid many unnecessary biopsies. Furthermore colposcopy has great importance as a method of teaching and investigating pathological changes of the ectocervix.

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COMPARISON BETWEEN CYTOLOGY AND COLPOSCOPY IN THE DIAGNOSIS OF EARLY CERVICAL CARCINOMA*

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FIFTY years ago, in the absence of unusual symptoms, the necessity for biopsy, and the site of biopsy, were determined by gross examination. Subsequently, extensive studies of the histologic patterns of early cervical carcinoma were reported by such men as Meyer,[1] Rubin,[2] Schauenstein,[3] Schiller,[4] and Schottländer and Kermauner.[5]

In 1925 Hinselmann[6] described the colposcope, an apparatus that permits stereoscopic observation of the cervix with bright illumination at ten or twenty times its normal size. Exact sites of abnormal epithelium are thus determined and a selective spot biopsy procured. Unfortunately, this method has been only sporadically accepted in various portions of the world. In 1943, Papanicolaou and Traut[7] published a monograph on the vaginal smear method as a means of early cancer detection. This latter method has rapidly attained wide popularity in the United States and elsewhere.

Relationships Between Colposcopy and Cytology

Both methods, colposcopy and cytology, have in common the necessity for histologic confirmation of their findings. The cytologic technique can localize the site of origin of cells only indefinitely. By colposcopy, provided that the lesion is accessible, the specific area of abnormality can be determined. In about 80 per cent of all examinations conducted in the outpatient department, colposcopy alone is sufficient to identify with certainty a macroscopically suspicious condition such as a glandular erosion of the portio or a benign stage of healing; in such case we believe biopsy to be superfluous. With cytology alone a cone biopsy with multiple sections is required for verification.

Carcinomatous changes are suspected when, in the stained cytologic smear, the exfoliated or abraded cells demonstrate changed morphology, especially abnormal nuclear morphology. By colposcopy there are five aberrations noted: simple leukoplakia, a whitish plaque which may or may not be visible to the naked eye; ground leukoplakia, a yellowish-white appearance with red stippling; mosaic leukoplakia, a yellowish-white appearance with a mosaic pattern; atypical blood vessels in the form of corkscrews or commas; and erosio vera, i.e., loss of surface epithelium. In the presence of such colposcopic changes, carcinoma in situ or early invasive malignancy is found in about 10 per cent of cases. The more pronounced the colposcopic changes,

*Presented at the Symposium on Applied Cytology of the International Union Against Cancer, Brussels, 1957.

both qualitatively and quantitatively, the greater is the likelihood of malignancy. Since both techniques, cytology and colposcopy, may give false positive and false negative results, it seems expedient to combine the two to achieve better results than can be obtained by either method alone.[8, 9, 10]

Some of the difficulties of correlating cytologic and colposcopic abnormalities with the histologic picture arise from the confused classification of cervical epithelial atypism and early carcinoma. Our own system of labeling proliferative epithelium follows: (1) *Epithelial dysplasia.* This comprises a hyperactivity of basal cells, at times on the basis of inflammation. These cases must be carefully followed since carcinoma may occasionally develop later. (2) *Carcinoma in situ.* This implies carcinoma-like cell changes in the entire thickness of the cervical epithelium with even extension in the cervical glands. The basal membrane, however, is intact. Cytologically this lesion may be indistinguishable from invasive carcinoma. (3) *Carcinoma in situ with questionable invasion.* This group, in our opinion, should not be included in Stage I carcinoma but should be considered separately. (4) *Early invasive carcinoma (Stage I).*

Experiences With Colposcopy and Cytology

Investigations on the efficiency of cytology and colposcopy in the diagnosis of early cervical cancer were carried out at the Universitäts-Frauenklinik, Hamburg. The greatest interest centered on carcinoma in situ. From Jan. 1, 1936, until April 1, 1957, 403 cases of carcinoma in situ were seen (Table I). From 1936 until 1945 the annual rate of detection was in the neighborhood of 4 cases per year, usually accidental findings from curettage and biopsy. By the addition of routine colposcopy with selective spot biopsy the number of diagnosed cases increased to about 15 yearly. With the subsequent addition of the smear technique used *routinely* 50 to 60 cases were discovered yearly.

Smears were obtained from the vaginal pool, from the cervical portio, and from the endocervical canal. The slides were fixed and stained by the method of Papanicolaou. After the smear was obtained, colposcopy was performed and a selective spot biopsy done as indicated. If colposcopy was negative, but the smear abnormal, the patient was hospitalized, and a curettage and coning cervical biopsy performed.

TABLE I. YEARLY DISTRIBUTION OF CARCINOMA IN SITU AT THE UNIVERSITÄTS-FRAUENKLINIK, HAMBURG

1936 through 1947	39 cases	Biopsy or curettage
1948	17 cases	Smear plus colposcopy with selective spot biopsy
1949	16 cases	
1950	16 cases	
1951	27 cases	Smear plus colposcopy with selective spot biopsy on *routine examination*
1952	48 cases	
1953	51 cases	
1954	54 cases	
1955	62 cases	
1956	57 cases	
1957 (up to April 1)	16 cases	
Total	403 cases	

Our results with colposcopy and cytology in 403 cases of carcinoma in situ are summarized in Table II. Three hundred and thirty-six cases were studied by colposcopy alone; 10 were negative by this method, an error of 3 per cent. Three hundred and thirteen cases were evaluated cytologically; 276 were positive or suspicious with 37 negative, giving an error of 11.1 per cent. Two

hundred and ninety-five cases were studied by both methods. Of these the result was positive by both methods in 253 cases. Thirty-four cases (25 with leukoplakia) were positive by colposcopy and negative by smear. It is likely that the surface keratinization formed a covering on the epithelial surface, thus lessening desquamation of abnormal cells. In 6 (3 of which were endocervical) the smear was positive and the colposcopic findings negative. There were 2 endocervical cases, not detected by either technique; these were found by incidental curettage of the canal.

TABLE II. EVALUATION OF 403 CASES OF CARCINOMA IN SITU

Studied by *colposcopy*		336 cases
Positive findings	326	
Negative findings	10	
Error	3%	
Studied by *cytology*		313 cases
Positive or suspicious findings	276	
Negative findings	37	
Error	11.1%	
Studied by *colposcopy and cytology*		295 cases
Both positive	253	
Positive colposcopy, negative smear	34	(of these 25 were cases of leukoplakia)
Positive smear, negative colposcopy	6	(of these 3 were endocervical)
False negatives by both methods	2	(2 endocervical)

The over-all results in the diagnosis of cervical carcinoma from 1945 to 1954 are outlined in Table III. By the combined use of both methods the incidence of Stage I increased from 18.4 to 36 to 40 per cent and Stage 0 (carcinoma in situ) from 4.2 to 27.7 per cent. This is an improvement on the 17.5 per cent of Carter and associates[11] who utilized the smear technique alone.

TABLE III. RESULTS OF DIAGNOSIS OF CERVICAL CARCINOMA (1945-1954)

METHOD	PERIOD	STAGES I-IV	NO. OF CASES	
			STAGE I	STAGE 0 (OF TOTAL OF STAGES 0 THROUGH IV)
Macroscopic excision or curettage, histology alone	1945-1947	407	18.4%	4.2% (18 cases)
Colposcopy with selective spot biopsy, cytology and histology	1948-1951	322	30.4%	19.1% (76 cases)
	1952	134	40.3%	26.4% (48 cases)
	1953	144	33.3%	26.1% (51 cases)
	1954	141	36.2%	27.7% (54 cases)

From these findings it is definitely shown how both methods despite, or because of, their differences support each other in an ideal fashion. The smallest atypical changes on the surface of the portio, which are not sufficiently marked to cause cytological changes on smear, can be clarified through colposcopy with selective spot biopsy. On the other hand, intracervical cases which cannot be diagnosed by colposcopy often give a positive test when the Ayre spatula is used. Without doubt, each technique in itself gives excellent results.

Summary

A comparison between the results of colposcopy and of cytology shows that these methods complement each other in ideal fashion in diagnosing early stages of carcinoma of the cervix uteri. With the smear method in carcinoma in situ cases there was an error of 11.1 per cent (out of 313 cases). This may

be due to the very small extent of the lesion. Colposcopy had a 3 per cent error (out of 336 cases of carcinoma in situ). By the combination of the two methods the incidence of carcinoma in situ was increased to 27.7 per cent, the Group I carcinoma to 36 to 40 per cent of all cervical carcinomas. To our knowledge, up to the present time, these figures have not been achieved by any worker with the smear method alone.

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THE MULTICENTRIC ORIGIN OF CARCINOMA IN SITU OF THE CERVIX

Case Report

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THE multicentricity of carcinoma of the cervix is occasionally mentioned in the current literature on the subject. Most authors seem to accept this postulate, but the evidence for it is scanty. The purpose of this case report is to present supportive evidence for the supposition of a multicentric origin of carcinoma in situ of the cervix and to demonstrate that in this case a conization of the cervix would have been inadequate as a curative procedure.

Mrs. N. G., Hospital No. 598787, was a 34-year-old white woman, gravida ii, para i, abortion i, who consulted her family physician 2 months prior to admission because of constipation. At that time a routine pelvic examination including a Papanicolaou test was done and a suspicious lesion of the cervix was cauterized. The smear was reported as suspicious of malignant process of the cervix and the patient was referred to The Ohio State University Cancer Clinic where a cervical biopsy was done on Oct. 9, 1956. Following the biopsy, the patient bled profusely and was admitted to the University Hospital on Oct. 13, 1956. A cold-knife conization and dilatation and curettage were done. Both the previous biopsy and conization specimen were reported by the pathologist as carcinoma in situ of the cervix. On Nov. 4, 1956, she was readmitted to the hospital and a total abdominal hysterectomy including removal of a vaginal cuff was performed. The postoperative course was uneventful.

Pathological Examination.—The first biopsy specimen consisted of fragments of cervical squamous epithelium with focal cellular pleomorphism, lack of maturation, and crowding of the cells. This was interpreted as indicative of carcinoma in situ. The second diagnostic procedure, namely, a wide and deep cervical cold-knife conization, revealed a circumscribed plaque of cervical carcinoma in situ flanked from below by normal squamous epithelium and from above by normal columnar endocervical epithelium. Because of an identical picture in all step sections throughout the conization specimen, one would be tempted to conclude that the lesion (carcinoma in situ) had been completely excised. Later the hysterectomy specimen displayed a baffling picture. The distal portion of the endocervical canal and the cervix itself showed granulation tissue covered partially by a regenerating normal cervical epithelium (Figs. 1*A*, 1*B*, 1*C*, and 2). This was the site of the previous cold-knife conization. No residual carcinoma in situ was found here. The upper portion of the endocervical canal was lined by entirely normal columnar epithelium (Figs. 1*D* and 1*E*); but high up and in close proximity to the internal os another focus of squamous-cell carcinoma in situ was found (Figs. 1*F* and 3) surrounded by normal intact columnar epithelium. Because this lesion was found within normal noninjured endocervical tissue, the conclusion was made that this lesion seated high in the endocervical canal represented another focus of carcinoma in situ. The finding

Figs. 1-3.—The composite picture demonstrates at the right (*1A, 1B, 1C*) a hemorrhagic area covered partially by regenerating squamous epithelium. This is the upper end of the previous conization site. The inset at the right (*2*) shows a closeup view of this area. The central part of the composite picture (*1D, 1E*) depicts the end of the injured area of the endocervical canal and to the left of this an intact, noninjured, nonregenerating endocervical mucosa with some glands. On the extreme left (*1F*) there is a rather typical picture of a squamous-cell carcinoma in situ. This area was located near the internal os. The inset at the left (*3*) demonstrates the essential characteristics of this carcinoma in situ. A similar picture was encountered in all "around-the-clock" step sections through the cervix after hysterectomy.

that this focus was indeed surrounded by normal nonregenerating and noninjured endocervical mucosa justifies the conclusion of a multicentric origin of the squamous-cell carcinoma in situ of the cervix in this case.

Summary and Conclusions

A case is presented of carcinoma in situ of the cervix detected by routine Papanicolaou smear, diagnosed by punch biopsy and cold-knife conization of the cervix, and treated by hysterectomy. Examination of the tissue removed gives evidence for the postulate of a multicentric origin of carcinoma in situ of the cervix and indicates that treatment by conization alone may not be sufficient for the removal of all malignant squamous epithelium in this disease.

We wish to thank Dr. William E. Copeland for permission to report this case.

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THE UTERINE ISTHMUS AND ITS SPHINCTER MECHANISM, A RADIOGRAPHIC STUDY

I. The Uterine Isthmus Under Normal Conditions

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IN A PREVIOUS communication[1] the syndrome of menouria following lower segment cesarean section was described and it was shown that its peculiar features could be accounted for by the presence of a functional sphincter at the uterine isthmus. The question of the isthmus and its sphincter mechanism has since been investigated in some detail and this investigation has yielded interesting information. Before describing our methods and results it is necessary to review the literature on this rather obscure topic.

Review of the Literature

The Uterine Isthmus.—Even at the present day there is no general agreement as to the very existence of the uterine isthmus as a distinct and specific entity. The concept of the isthmus was introduced as a result of the classical work of Aschoff,[2] although this term had earlier been used by Wigand[3] and Waldeyer.[4] Aschoff described the isthmus as a distinct part of the uterus 8 to 10 mm. in length lying between the body and the cervix and bounded superiorly by the orificium internum anatomicum and inferiorly by the orificium internum histologicum. This view was later substantiated by the important studies of Stieve[5, 6] and Frankl.[7] The latter observer stated that with skill the upper and lower limits of the isthmus can always be defined both anatomically and histologically. He found that the mucosa of the isthmus differs from that of the corpus in the different phases of the menstrual cycle and maintained that the isthmus has an independent vasculature, a fact which he considered in harmony with the individual physiological life of this section of the womb. Other authorities,[8-10] however, continued to regard the uterus as composed of only two parts, the corpus and the cervix.

In recent years most authors[11-16] have come to accept Aschoff's view and some[17-19] have even considered the question to be finally settled, but others[20-22] have again seriously challenged the isthmic concept and claimed that the isthmus should be considered a part of the corpus uteri. Danforth and Chapman[21] concluded on anatomical grounds that the concept of the isthmus as an autonomous entity should be discarded while Gross[22] arrived at the same conclusion, mainly because he thought that the isthmus had no specific function. In fact, the isthmus has hitherto been regarded, even by those who believe in its existence, as a part which serves no function in the nongravid uterus but from which the lower segment is formed during pregnancy and labor. It is not therefore surprising that many standard works on gynecology do not even mention the uterine isthmus.

The Sphincter at the Corporeocervical Junction.—Anatomical studies have failed to show that a sphincter, in a strict anatomical sense, is present between the corpus and the cervix but have strongly suggested that the distribution and arrangement of the muscle fibers in this region are such that they can and do function like a sphincter. This "sphincter isthmii interni" was described as far back as 1872 by Lott.[23] Half a century later Oertel[24] emphasized the presence of a functional sphincter at the internal cervical os. Stieve[6] found that in the isthmic segment the muscle fibers were much more abundant and lay closer to each other than they did in the cervix. Schroeder[25] noted that the uppermost portion of the cervical wall contained spirals of muscles which formed a ring tightly surrounding the mucosa and causing marked narrowing of the canal.

More recently Danforth[20] found that as one ascends the cervix to the region of the histological internal os a level is reached where the predominance of fibrous tissue ceases, giving way to smooth muscle. Hughesdon[26] agreed with Danforth on this particular point and stated that "it may be doubted whether structure and function need necessarily correlate well here, for randomly arranged muscle bundles, if packed into the gross form of a ring and obliged to contract together might be able to act as a compressor." Exactly the same viewpoint was expressed by Asplund[27] and by Wendell-Smith,[28] who argued that "the overall effect of contraction of a ring of interlacing fibres will be sphincteric."

Dissections of pregnant uteri have shown that the sphincter mechanism above the cervix is even better developed and more marked during pregnancy.[26, 28-31] The analogy has been noted between the sphincter at the internal cervical os and the tubal and pyloric sphincters where a sphincter action exists despite the anatomical absence of a true sphincter muscle.[32-35]

Recent experimental studies have fully confirmed the assumption that the muscle fibers at the junction of corpus and cervix have a sphincter action.[34, 36-40] It has further been shown that the tone of this sphincter is susceptible to hormone influences,[27, 40] undergoes certain variations in the course of the menstrual cycle,[27, 38-40] and can be modified by drugs which act on the autonomic system.[37] In vitro examination of the spontaneous motility of muscle strips from the uterus has revealed that in the premenstrual phase of the cycle the transverse muscle strips from the isthmus, but not from any other part of the uterus, show a very characteristic motility pattern of a "sphincteric type."[41, 42]

It is apparent that there is unanimous agreement among workers on the subject that a functional sphincter exists at the junction of the corpus and the cervix both in the pregnant and in the nonpregnant states. Although the significance of this sphincter in pregnancy, abortion, and labor has been discussed by several authors[26, 28, 39, 43-46] little is known of its normal or disordered function in the nongravid uterus. No wonder, therefore, that no reference to its existence could be found in any of the well-known textbooks of gynecology. Who indeed would care for a functional sphincter that seemed to have no function under normal or abnormal conditions!

Material and Methods

Sixty normal women were investigated, including 3 who were postmenopausal, 2 in early pregnancy, and 55 nonpregnant women in the childbearing age (34 nulliparous and 21 parous). Many of these had come to seek advice for sterility but patients were included in this group only if they were menstruating regularly and painlessly, showed no obvious gynecological abnormality, and had had no previous dilatation of the cervix. Two methods of investigation were employed.

Method A (Isthmography).—In ordinary hysterosalpingography the isthmic region is not visualized because the cannula is usually introduced right into the isthmus or even into the uterine cavity. The literature contains few reports on the radiographic pictures of the cervix[47–54] and occasional references to the radiographic appearance of the internal os[33, 39, 51] but, to our knowledge, only one comprehensive radiographic study of the uterine isthmus has so far been reported.[27] Even in detailed monographs and atlases dealing with hysterosalpingography, little or no mention of the isthmus is found.[50, 55]

A modified technique was employed to study the isthmic segment to which we have given the name "isthmography." An ordinary Jarcho cannula was used but special rubber cones of different sizes were designed so that although only 1 to 1.5 cm. of the cannula was introduced into the cervical canal the external os could be efficiently closed and no leakage occurred. When the tip of the rubber cone could not properly occlude the cervical os, a special screw-tipped cannula was used to close the cervix with care not to screw it more than 1 to 1.5 cm. up the cervical canal. Since the cervical canal is 3 to 4 cm. long,[48, 51] this technique allowed visualization of the upper part of the cervix and the entire isthmus. Four to five cubic centimeters of Lipiodol was injected according to whether the woman was nulliparous or parous. It was found that Lipiodol gave more satisfactory pictures of the isthmic segment, although more viscid media may give better pictures of the cervix. It soon became evident that certain technical details are important if the region of the isthmus is to be properly studied. No sedative or antispasmodic drug should be given before the test. The examiner should wait for 5 minutes after holding the cervix with forceps and introducing the cannula before the injection is made. The Lipiodol should be warmed to body temperature and should be injected as slowly as possible.

In 5 cases a dilator of suitable size was introduced into the cervix and the point at which it encountered resistance was noted. By a small sharp curette 2 pieces of mucosa were removed one from just below and the other from just above the marked point. In order to define the position of this point on the radiograph it was in one case marked by a small metal clip during a vaginal suspension operation and isthmography was performed a few days later.

Isthmography was performed on 40 of the 55 nonpregnant women in the childbearing age. In 16 cases it was carried out during the follicular phase of the cycle, in 12 cases during the luteal phase, and in 8 cases just one or 2 days before the onset of menstruation. In 4 cases it was done on all 3 occasions. When it was performed in the luteal phase or just before menstruation we usually verified the occurrence of ovulation by endometrial biopsy but in some private cases typical basal temperature records were relied upon. Isthmography was also used in the investigation of the 3 postmenopausal and the 2 pregnant women in this series.

Method B (Direct Hysterography).—This method was inspired by two previous experiments. Keiffer[56] injected water into the uterine horn of dogs and found that it remained inside the uterus up to a pressure of 30 to 40 cm. of water if the spinal cord was intact. Westman[34] injected Lipiodol inside the uterine cavity during an abdominal operation. His illustrations of the case show that the oil remained inside the uterus for 2 hours and some of it was still present 5 hours after the injection. This confirmed his finding by manometric insufflation that there is a sphincter between the corpus and the cervix. He did not, however, indicate the phase of the menstrual cycle in which this experiment was made or the manner in which the uterus eventually emptied itself. Initially we injected Lipiodol through the uterine wall into the uterine cavity

by means of a fine lumbar-puncture needle in the course of the operation of vaginal suspension. Because it seemed possible that the anesthesia or the operative manipulations might alter the behavior of the uterus, an original technique was subsequently devised.

In cases of retroverted uterus, a long, fine needle was introduced without anesthesia through the posterior fornix and through the wall of the retroverted uterus into the uterine cavity. After some experience it was not difficult to feel the sudden disappearance of the resistance of the uterine wall when the tip of the needle reached the uterine cavity, at which point the Lipiodol was slowly injected and the needle withdrawn. If the uterus was anteverted, a very small posterior colpotomy incision was made under local anesthesia and a long fine needle slightly curved anteriorly was introduced and guided by the finger through the posterior wall of the uterus into the uterine cavity. Lipiodol was then injected, the needle withdrawn and the colpotomy incision closed by two stitches. No complications occurred although in 2 of the earlier cases it seemed that a little oil was injected into the uterine wall for slight venous intravasation was noted in the radiograph. Because different degrees of uterine distention produce different effects on uterine tone and contractility,[57-59] the same amount of Lipiodol was used in all cases, namely, 2 c.c. for nulliparous and 2.5 c.c. for multiparous women. Serial spot films were made at intervals after the injection. In most cases a clip was placed on the anterior lip of the cervix at the external os to mark its position on the radiograph.

Method B was performed on 15 of the normal nonpregnant women in the childbearing age. It was carried out 5 times in the follicular phase of the cycle, 5 times in the luteal phase and 5 times one or two days before the onset of the period.

Results

A. Isthmography.—In all the cases investigated the isthmic canal was visualized on the radiograph as a distinct segment of the uterus narrower than the cervical canal below and the corporeal cavity above. There was no difference in the appearance of the isthmus in nulliparous and parous women. If the aforementioned precautions were observed during the injection, the isthmic canal was almost always seen to be bounded by a definite constriction superiorly and another definite constriction inferiorly which appeared very similar to those seen radiographically at the sites of the tubal and the pyloric sphincters. It will be seen that the appearance of these two constrictions and their behavior under normal and abnormal conditions justify the conclusion that they are caused by the presence of an upper sphincter between the corpus and the isthmus and a lower sphincter between the isthmus and the cervix. These two sphincters will henceforth be referred to as the superior isthmic sphincter (SIS) and the inferior isthmic sphincter (IIS) respectively.

In normal women of childbearing age the isthmic canal during the follicular phase of the cycle appeared cylindrical in shape (Figs. 1 and 2). The constrictions marking SIS and IIS appeared of equal size, indicating that the tone of the two sphincters was similar. In the case illustrated in Fig. 2, a clip was used to mark the point where a dilator introduced into the cervical canal encountered resistance, as previously described. It can be seen that this point exactly coincides with the site of IIS. Examination of strips of mucosa removed from below and from above the resistance point in this and in other cases always showed that the mucosa below it was typical cervical mucosa while the mucosa above it was similar to that which lines the isthmus.[2, 7] This shows that IIS is situated at the level of the histological internal os of Aschoff.

During the luteal phase of the cycle the isthmic segment usually appeared longer and was always markedly narrower than during the follicular phase (Figs. 3 and 4). Its width on the film seldom exceeded 1 mm. and it sometimes was so narrow that it was hardly visible (Fig. 4). The two constrictions could still be seen and their appearance indicated that SIS and IIS were now more tightly closed than during the follicular phase.

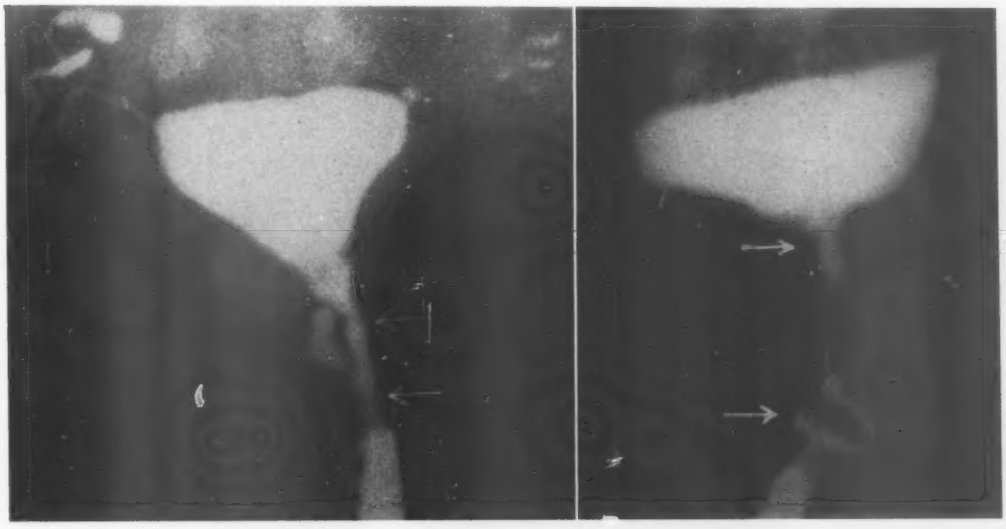

Fig. 1. Fig. 2.

Figs. 1 and 2.—Isthmography in follicular phase of cycle. The isthmus appears cylindrical in shape. Arrows indicate sites of SIS and IIS. Clip in Fig. 2 corresponds to position of IIS as explained in text.

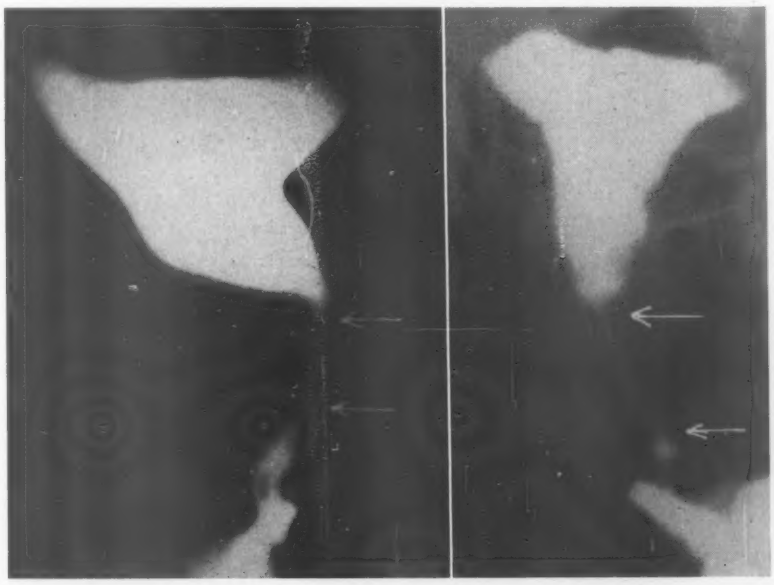

Fig. 3. Fig. 4.

Figs. 3 and 4.—Isthmography in luteal phase of cycle. SIS and IIS are both contracted and the isthmic canal is long and narrow.

In the 2 days immediately preceding menstruation, the appearance of the isthmic segment was found to undergo a marked change. This was first accidentally noted in a patient who happened to be examined on the day before the period and was later confirmed in the others examined at that particular time, including 4 patients in whom isthmography was carried out both at the height of the luteal phase and in the immediate premenstrual phase. In this latter phase the isthmic segment became definitely shorter and wider and both SIS and IIS became obviously relaxed, the relaxation being usually more marked in the superior than in the inferior sphincter (Figs. 5 and 6).

Fig. 5.

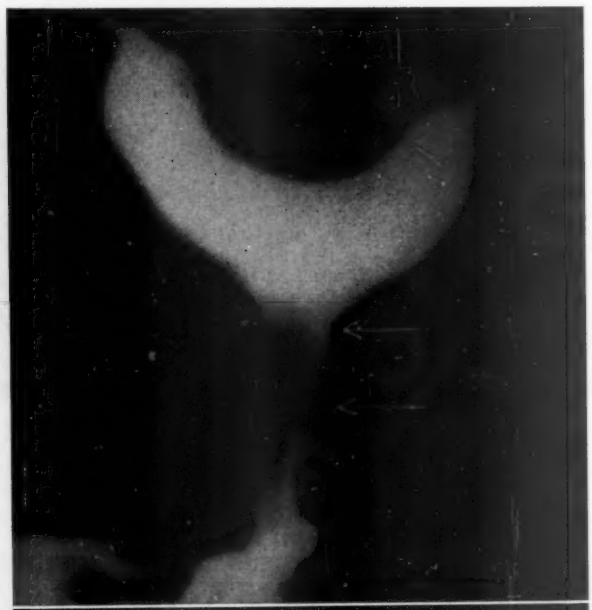

Fig. 6.

Figs. 5 and 6.—Isthmograpny on the day before onset of menstruation. SIS and IIS are now markedly relaxed and the isthmus is short and wide.

In the 3 postmenopausal women examined the isthmus was seen to be dilated and ill defined but in 2 of them the constrictions marking SIS and IIS were still

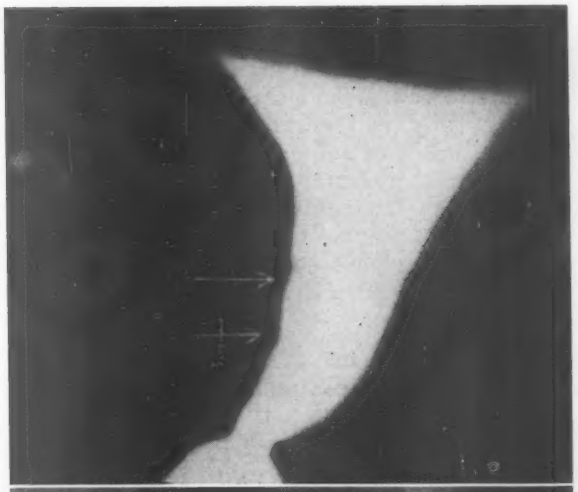

Fig. 7.

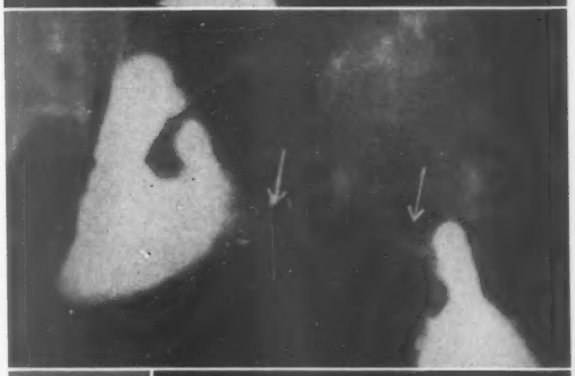

Fig. 8.

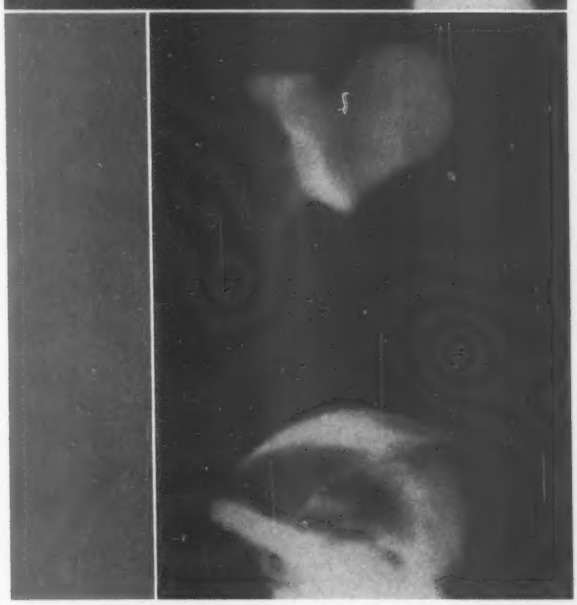

Fig. 9.

Fig. 7.—Isthmography in a patient 3 years past the menopause. The isthmus appears very wide and SIS and IIS are barely recognizable.

Fig. 8.—Isthmography in first month of pregnancy. The isthmus is elongated and very narrow and both SIS and IIS are tightly closed. Uterus in this case was deviated to the right.

Fig. 9.—Isthmography in a woman 8 weeks pregnant. Same appearance of isthmus as in Fig. 8. Some leakage of Lipiodol occurred during injection before isthmic resistance was overcome.

recognizable (Fig. 7). In 2 cases isthmography was performed in early gestation. The 2 pregnancies, one of 4 and the other of 8 weeks' duration, went on undisturbed. Hysterography was carried out on pregnant women by some previous workers,[27, 55, 60] and was indeed suggested as a method of diagnosis of early gestation.[60] In our 2 pregnant patients the isthmic canal appeared markedly elongated and very narrow (Figs. 8 and 9). Unusual resistance was encountered during the injection of Lipiodol and some leakage occurred before this resistance of the isthmic sphincters was overcome (Fig. 9). The changes looked like an exaggeration of the characteristic appearances of the luteal phase of the menstrual cycle.

B. Direct Hysterography.—When 2 to 2.5 c.c. of Lipiodol was injected into the uterine cavity by Method B the oil remained within the corpus for some time, which confirmed Westman's[34] conclusion that the uterine cavity is a space normally closed by the tubal and the isthmic sphincters. We wanted to determine when and how the uterus emptied itself in the different phases of the menstrual cycle. The difficulty in timing the spot films to this effect can be readily appreciated. However, very characteristic patterns were noted which will now be described.

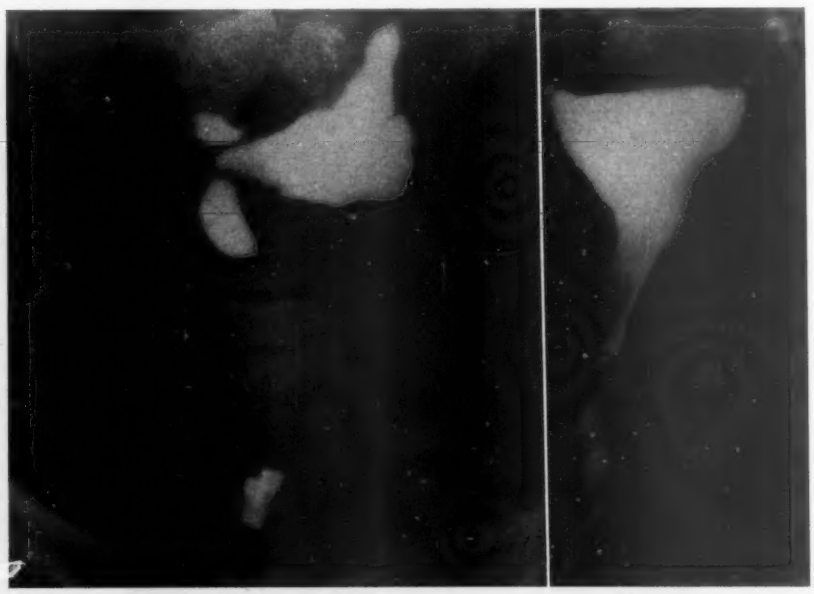

Fig. 10. Fig. 11.

Fig. 10.—Direct hysterography in follicular phase of cycle. Film made one hour after injection shows Lipiodol still in uterine cavity. Distance of uterine shadow from clip at external os indicates that the Lipiodol is detained at level of SIS. In this case slight venous intravasation occurred.

Fig. 11.—Direct hysterography in follicular phase of cycle. Film made 3 hours after injection shows Lipiodol passing through the tubes and through the isthmus and cervix.

During the follicular phase of the cycle, the Lipiodol remained inside the uterus for 1 to 3 hours (Fig. 10). When the uterus then emptied itself this occurred both through the isthmus and the cervix into the vagina and through the Fallopian tubes into the peritoneal cavity (Fig. 11). It could not be determined with certainty whether the Lipiodol passed first into the cervix or into the tubes.

During the luteal phase the oil remained inside the uterine cavity for 4 to 8 hours or even longer. The uterus then always emptied itself through the

tubes into the peritoneal cavity and no Lipiodol passed into the vagina. (In all the patients examined at least one tube was patent.) In some cases the film taken after evacuation showed the radiopaque material already present in the peritoneal cavity (Fig. 12) but in others the Lipiodol was actually seen passing through the tubes (Figs. 13 and 14).

When the method was carried out one or 2 days before the period the oil was retained inside the uterus for only 10 to 30 minutes. Evacuation then occurred through the cervix into the vagina (Fig. 15) and no Lipiodol escaped into the tubes. Evacuation of the uterus sometimes occurred before a film could be taken but the oil could be seen passing from the cervix and subsequent radiography showed that no radiopaque material was present in the peritoneal cavity.

Fig. 12.

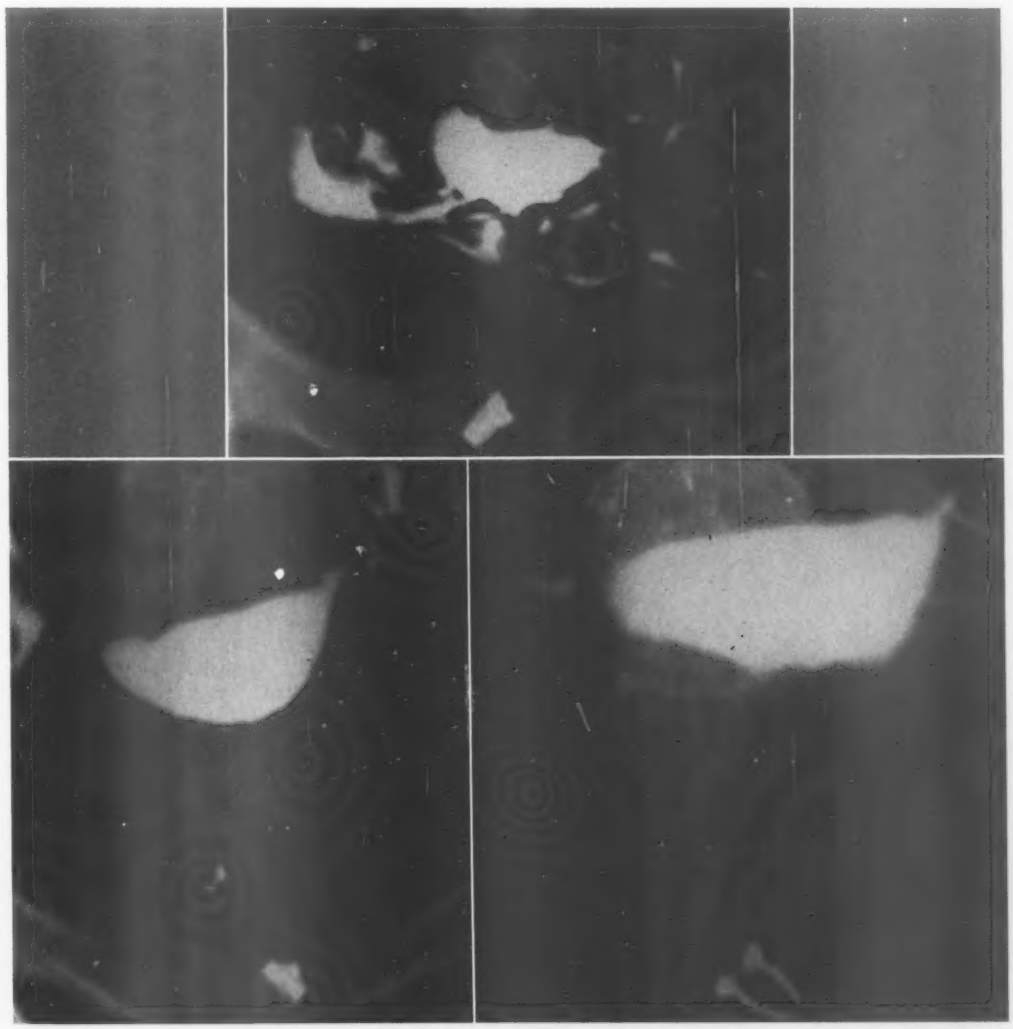

Fig. 13.

Fig. 14.

Fig. 12.—Direct hysterography in luteal phase of cycle. Film made 8½ hours after injection shows Lipiodol dispersed into the peritoneal cavity.

Figs. 13 and 14.—Direct hysterography in luteal phase of cycle. Films made 5½ hours after injection in one case and 7 hours after injection in another show Lipiodol passing through the tubes but not through the isthmus.

Comment

A. Isthmography.—Our finding that the isthmus is narrowed during the luteal phase of the cycle is in agreement with the conclusions of Asplund[27] and explains Palmer's[39] observation that the isthmic tone is higher during the luteal than during the follicular phase. These two observers ascribed this finding to the effect of progestin on the isthmic musculature, a conclusion with which we are in full agreement. The isthmic musculature is susceptible to hormone action[40] while the isthmic mucosa does not undergo any significant change during the luteal phase.[7]

The shortening and widening of the isthmus and the relaxation of its sphincters which occur in the immediate premenstrual phase have never before been described. This is probably because in the only systematic radiographic study of the isthmus thus far reported[27] no examinations happened to be made at that time. These changes must also be due to endocrine factors.

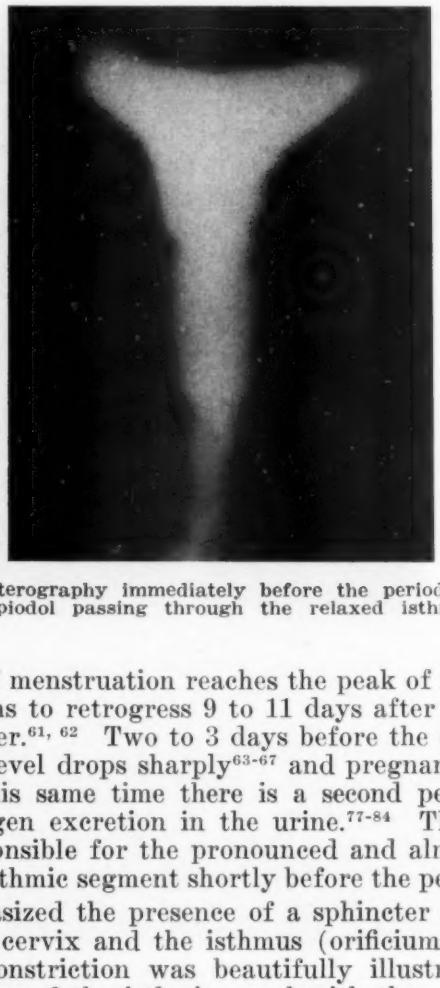

Fig. 15.—Direct hysterography immediately before the period. Film made 20 minutes after injection shows Lipiodol passing through the relaxed isthmus but not through the tubes.

The corpus luteum of menstruation reaches the peak of its activity 7 to 9 days after ovulation, begins to retrogress 9 to 11 days after ovulation, and is nonfunctional 4 days later.[61, 62] Two to 3 days before the onset of menstruation, the blood progestin level drops sharply[63-67] and pregnanediol disappears from the urine.[68-75] At this same time there is a second peak of estrogen in the blood[76] and of estrogen excretion in the urine.[77-84] These hormone changes are presumably responsible for the pronounced and almost sudden alteration which occurs in the isthmic segment shortly before the period.

Asplund[27] emphasized the presence of a sphincter at the site of the constriction betwen the cervix and the isthmus (orificium isthmi inferius). Although the upper constriction was beautifully illustrated in many of his figures at the junction of the isthmic canal with the corporeal cavity which he termed "orificium isthmi superius," he did not ascribe it to a sphincteric action but to the possible presence of mucosal folds. This explanation is obviously erroneous for marked relaxation occurs in this region shortly before

the period when the endometrium is still at the height of its secretory reaction. The upper constriction could be seen in all phases of the cycle provided that no sedative or antispasmodic was given and the Lipiodol was injected gently and slowly. It could even be defined during pregnancy and in postmenopausal women with atrophic endometrium. Its appearance is identical with the lower constriction and with the constrictions seen radiographically at the sites of the tubal and the pyloric sphincters.

The superior isthmic sphincter has not heretofore been demonstrated in the human uterus although its presence has been suspected[45] on comparative anatomical grounds. Both in the uterus simplex of the monkey and in the uterus duplex of the dog and sheep two definite sphincters are present, one at the upper and one at the lower boundary of the part of the uterus homologous to the lower segment or isthmus.[43, 45, 85] In the laboring human uterus a constriction ring most commonly develops at the junction of the upper and lower segments or at the junction of the latter with the cervix. It has therefore been argued that, if there are no sphincters in the human uterus, the occurrence of constriction rings may represent at least an atavistic tendency in that direction.[45]

The widening and relaxation of the isthmus after the menopause can be explained by the atrophy of its musculature with the decline of ovarian function. On the other hand, the marked narrowing and elongation of the isthmic segment observed in pregnant patients must be due to the prolonged and intensified action of progestin secreted by the corpus luteum of pregnancy.

B. Direct Hysterography.—The pilot experiments performed by this method have also shed some light on the physiology of the uterus and its sphincters.

Uterine activity: The uterus always evacuated itself more rapidly during the follicular than during the luteal phase of the cycle, indicating that the tone and contractility of the corpus are more pronounced in the former than in the latter. Estrogen is known to increase the activity of the uterus in animals[86-89] and in man.[90, 91] In animals it was definitely established that the corpus luteum inhibits the spontaneous activity of the uterus and its reactivity to Pituitrin.[92-97] This action is brought about by the hormone progestin.[97-100] Uterine tokography in the human has, however, yielded conflicting results. Knaus[101, 102] observed that in the latter half of the cycle the spontaneous contractility of the uterus and its reactivity to Pituitrin were less than during the first half and attributed this to the action of progestin. Other workers[103-108] obtained different or opposite results. In a critical review of the literature Reynolds[58] came to the conclusion that the Knaus data are essentially valid and that the reports to the contrary must be regarded as presenting a modified picture of activity obtained under special conditions of recording. He remarked that one must consider what the apparatus does to the uterus as much as what the uterus does to the apparatus. The technique we used in Method B is perhaps the first attempt to investigate this question without the introduction of any balloon or other apparatus through the cervix. Our results confirm the Knaus-Reynolds contention that the uterus is considerably more quiescent during the luteal than during the follicular phase.

Shortly before the period the uterus was found to become active again and to evacuate itself even more rapidly than during the follicular phase. This coincides with the marked relaxation of the isthmus and with the sharp drop in the progestin and the marked rise in the estrogen level which occur 2 to 3 days before the onset of menstruation. It is interesting to compare the clinical results reported by Dickinson,[109] who carried out repeated rectal examination on a group of healthy women through several successive cycles.

He found that from about the ninth to the sixteenth day the uterus became increasingly active. Then as the cycle passed into the postovulatory phase the uterus again became quiescent until about 2 days before the onset of menstruation, when slight but definite contractions began which reached their height when menstruation became established.

Sphincteric activity: During the luteal phase of the cycle and provided one or both tubes are patent, the uterus empties itself through the tubes into the peritoneal cavity and no Lipiodol passes through the superior isthmic sphincter (Figs. 13 and 14). This corresponds with the finding by isthmography that the isthmus is most contracted during this phase of the cycle. In the immediate premenstrual phase the uterus evacuates itself entirely through the isthmus and cervix into the vagina and no Lipiodol passes through the tubes. Here the uterine isthmus appears most relaxed although both isthmic sphincters are still recognizable (Fig. 15). The tubal sphincters are tightly closed, probably to prevent regurgitation through the tubes during menstruation. Liesse[37] had observed that the tubal and isthmic sphincters reacted in an opposite manner to the injection of certain drugs. During the follicular phase of the cycle an intermediate situation is present. The uterus then seems to empty itself as easily through the tubal as through the isthmic sphincters.

The tone of the isthmic sphincters thus appeared to be highest during the luteal phase, lower during the follicular phase, and lowest immediately before the period. These findings are consistent with some previous clinical and experimental observations.[38] It can be seen that the behavior of isthmic activity in the different phases of the cycle is exactly opposite to the activity of the corpus. These two segments of the uterus also react in the opposite way to the administration of certain drugs.[37] This is not to be regarded, however, as functional antagonism[37] but rather as well-coordinated synergism.

Conclusions

The isthmus is structurally and functionally an autonomous portion of the uterus separated by a sphincter at the level of the anatomical internal os from the uterine corpus and by another sphincter at the level of the histological internal os from the uterine cervix. The sphincter mechanism of the isthmus keeps the uterine cavity at all times closed from below and prevents the access of organisms from the vagina and cervix. In this respect it is probably a more efficient barrier than the renowned cervical mucus plug. The relaxation of the isthmus during the period explains the frequency of ascending infection, e.g., by the gonococcus, after menstruation.

During the follicular phase of the cycle and at the time of ovulation the isthmic sphincters are relatively lax, thus facilitating sperm migration into the uterus. It has been suggested[27] that the rhythmic contractions of the isthmic sphincter exert a sucking action which plays a part in the transport of spermatozoa. It has also been reported[110] that uterine dyskinesia may interfere with sperm migration. It is therefore possible that temporary spasm of the isthmic sphincters may account for some cases of apparently causeless infertility.

During the luteal phase the isthmic sphincters become tightly contracted. This, together with the synchronous inhibition of the activity of the corpus, certainly provides the ideal conditions for the implantation and early growth of the ovum should fertilization occur. It is logical to assume that disorder of this function may favor low implantation of the ovum, perhaps in the

isthmus, or may even be responsible for very early unrecognized abortion. In early gestation the isthmus was found to be even longer and narrower than during the luteal phase. This is undoubtedly due to the progestin secreted by the corpus luteum of pregnancy and is of fundamental importance in protecting and supporting the ovum. The beneficial action of progestin in some cases of threatened abortion may be due, at least in part, to its effect on the uterine isthmus.

When fertilization of the ovum does not occur, the isthmus is prepared for the process of menstruation. Its sphincters become more relaxed than during any other phase of the cycle at the time when corporeal activity becomes most marked. When this physiological coordination exists menstruation is normal and painless. The relaxation of the isthmus during menstruation also facilitates the passage of the menstrual discharge through the cervix and helps to prevent tubal regurgitation.

Summary

1. The methods of isthmography and direct hysterography have been used to study the living anatomy and the physiology of the uterine isthmus in 60 normal women.

2. The isthmus is a distinct part of the uterus separated by a superior sphincter from the corpus above and by an inferior sphincter from the cervix below.

3. The isthmus is functionally independent from the corpus. The sphincteric mechanism of the isthmus is most contracted in the luteal phase of the menstrual cycle and most relaxed immediately before and during menstruation. The uterine corpus, on the contrary, is least active in the former phase and most active in the latter.

4. The coordinated activity of these two segments of the uterus is fundamentally important for the normal functions of fertilization, nidation, maintenance of pregnancy, and menstruation.

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THE UTERINE ISTHMUS AND ITS SPHINCTER MECHANISM, A RADIOGRAPHIC STUDY

II. The Uterine Isthmus Under Abnormal Conditions

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VERY little is known about the role of the uterine isthmus in pathological conditions. Weakness of the region of the isthmus was deemed responsible for alterations of position and attitude of the uterus.[1] When the endometrium of the uterus is hyperplastic in cases of metropathia hemorrhagica, or thick and edematous due to congestion, these changes are said to stop short at the anatomical internal os and the mucosa of the isthmus remains unaffected.[2] In adenomyosis uteri the region of the isthmus is very rarely involved but tuberculosis of the endometrium spreads unhindered to involve the isthmic segment and so usually does carcinoma after some initial resistance.[2] Large fistulas in the isthmic region may rarely be found in cases of tuberculosis of the cervix and the isthmus.[3] Infection following labor or cervical dilatation may cause permanent stenosis of the lumen of the internal os.[3] On the other hand, laceration and abnormal gaping of the internal os may follow overzealous dilatation and curettage, vaginal hysterotomy, traumatic delivery, cesarean section, or precipitate labor.[4-7] This entity has recently been emphasized as a cause of repeated abortion in the second trimester of pregnancy and certain operations have been devised to correct the abnormality both in the nonpregnant[4, 6] and in the pregnant[8-10] states. This thesis, however, has been strongly contradicted by some authorities[11, 12] who believe that the maintenance of pregnancy is a function of the cervix and not of the isthmus or the internal os.

This is about all the information that could be gleaned from the literature on the morbid anatomy of the isthmic region and the references to its morbid physiology are even much scantier. Certain observers maintain that neuromuscular derangements of the isthmus may cause gaping of the internal os and may therefore be responsible for some cases of abortion.[5] Spasm of the internal os as an etiological factor in primary dysmenorrhea was suggested by some authors[13, 14] and denied by others.[3]

Our finding[15] that the uterine isthmus plays an important part in the regulation of the process of menstruation and in the maintenance of pregnancy has prompted us to investigate its possible role in derangements of these particular functions.

Material and Methods

Forty abnormal cases were studied, including (a) 6 cases of secondary amenorrhea of more than one year's duration with atrophic endometrium and markedly hypoestrogenic vaginal smears; (b) 5 cases of metropathia hemorrhagica; (c) 3 cases of proved anovular menstruation one of which had normal and 2 hyperestrogenic smears; (d) 6 cases of "silent" habitual abortion in the second trimester of pregnancy with no discernible cause and with a history suggestive of incompetence of the internal os[6, 10] (In 2 of these cases there had been no previous labors or operations and 4 were cases of secondary habitual abortion.); (e) 20 cases of severe primary (essential) dysmenorrhea.

The methods of isthmography and direct hysterography have already been described and the results of their use in the study of the isthmus and its sphincter mechanism under normal conditions were reported in detail.[15] In isthmography the region of the isthmus is outlined by the injection of Lipiodol by a special technique in which the cannula is introduced for only a short distance into the cervix but leakage from the external os is prevented and certain precautions are taken to prevent abnormal dilatation or spasm of the isthmic sphincters. In direct hysterography 2 to 2.5 c.c. of Lipiodol is injected directly into the uterine cavity by a special long, fine needle introduced through the posterior fornix or through a small posterior colpotomy incision and serial radiographs are made at intervals to determine when and how the uterus evacuates itself.

All the patients in this group were examined by isthmography with the exception of 8 with primary dysmenorrhea. The effects of hormone administration were studied in the amenorrhea group. Three patients were examined before and after the administration of 4 doses of 20 mg. progestin given intramuscularly every other day. The 3 other amenorrheic patients were given the same dosage of progestin after priming with estrogen (5 intramuscular doses of 5 mg. estradiol benzoate over a period of 2 weeks). The effect of administration of estrogen alone was not observed. The 5 patients with metropathia hemorrhagica were examined during a nonbleeding episode. Of the 3 patients with anovular menstruation 2 were examined 7 to 8 days before the period and one was examined on the day before menstruation. Of the 6 cases of habitual abortion, 2 patients were examined during the follicular phase of the cycle and 4 at the height of the luteal phase. Twelve patients who had primary dysmenorrhea were examined by isthmography. The method was performed 4 times during the follicular phase of the cycle, 4 times during the luteal phase, and 6 times one or two days before the onset of menstruation. (In 2 cases it was done both in the luteal phase and shortly before the period.)

Direct hysterography was performed in 3 of the cases of habitual abortion during the luteal phase of the cycle; all 3 had also been examined by isthmography. Direct hysterography was also performed in 8 cases of primary dysmenorrhea; 2 of these patients were examined in the follicular phase, 3 in the luteal phase, and 3 shortly before the onset of the menstruation.

Results

Isthmography.—In the cases of secondary amenorrhea the isthmic canal was wider than normal and both the superior isthmic sphincter (SIS) and the inferior isthmic sphincter (IIS) were relaxed (Fig. 1). When progestin was given after priming with estrogen, the isthmic canal always became markedly narrower and both SIS and IIS more tightly closed (Fig. 2). The administration of progestin alone to 3 amenorrheic patients with low estrogenic function

brought about no change whatever in 2 cases but in one case it caused definite constriction of the superior isthmic sphincter (SIS) while the rest of the isthmus and the inferior isthmic sphincter (IIS) remained unchanged (Fig. 3). Asplund[3] had found that the administration of progestin alone to 4 cases of amenorrhea resulted in narrowing of the isthmus but he did not indicate their estrogenic function and in one case he actually mentioned that the endometrium was proliferative.

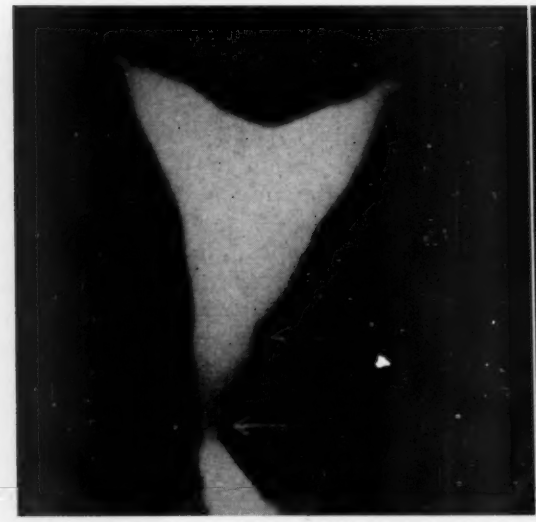

Fig. 1.

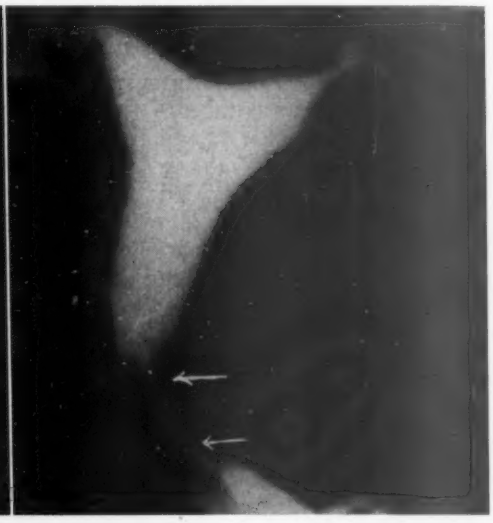

Fig. 2.

Fig. 1.—Isthmography in a case of prolonged amenorrhea. The isthmus appears wide. Arrows mark positions of superior isthmic sphincter (SIS) and inferior isthmic sphincter (IIS) which are both relaxed.

Fig. 2.—Same case as shown in Fig. 1 after treatment with estrogen followed by progestin. The isthmus became much narrower and both SIS and IIS tightly closed.

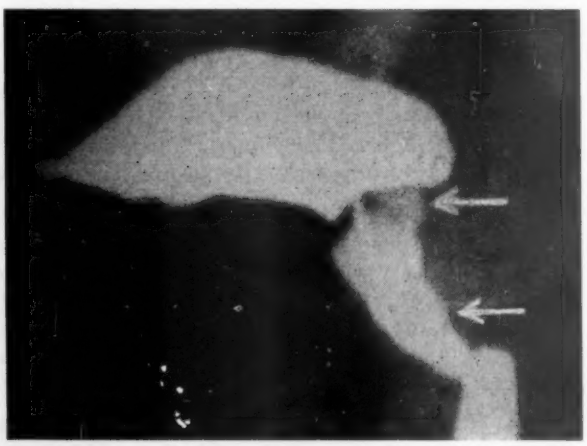

Fig. 3.—Peculiar appearance of isthmus in a patient with amenorrhea who received progestin alone. Contraction of SIS while the rest of the isthmus and IIS remained unaffected.

In the cases of anovular menstruation isthmography performed one week before the period showed a dilated isthmic segment with relaxed sphincters

(Fig. 4). This appearance is quite different from the normal constricted appearance of the isthmus during the luteal phase of the ovulatory cycle. In the cases of metropathia hemorrhagica the isthmic canal was very wide and merged almost imperceptibly with the uterine cavity above and the dilated cervical canal below, with only a faint suggestion of the positions of SIS and IIS (Fig. 5). The body of the uterus had a shaggy, irregular contour due to the hyperplastic

Fig. 4.

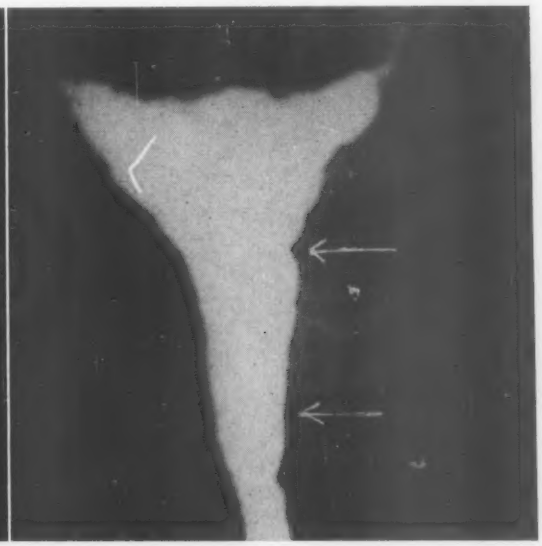

Fig. 5.

Fig. 4.—Case of anovular menstruation one week before period. The isthmus is wide and both sphincters are relaxed.

Fig. 5.—Case of metropathia hemorrhagica. The isthmus and its sphincters are markedly dilated. The shaggy contour of the hyperplastic endometrium ends sharply at the level of SIS.

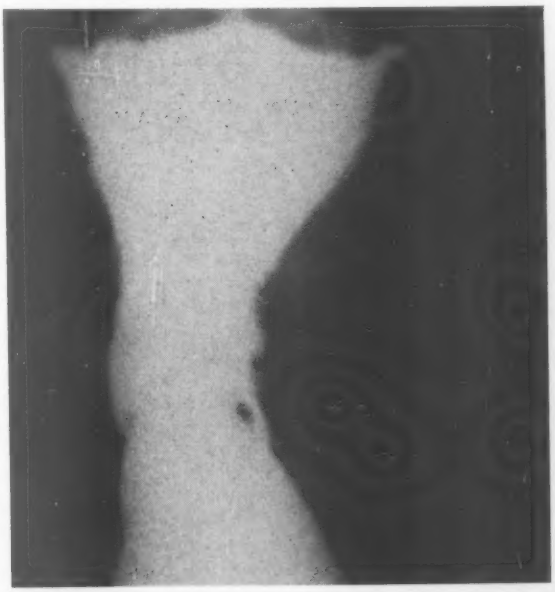

Fig. 6.—Case of habitual abortion due to incompetence of the isthmus examined in luteal phase of cycle. The isthmus is very wide and its sphincters cannot be identified.

polypoid endometrium which stopped sharply at the level of SIS. Since pathological studies[2] had shown that in cases of metropathia the endometrial hyperplasia always stops short of the isthmus at the level of the anatomical internal os of Aschoff, the radiographic appearances indicate that SIS is situated at this level.

Fig. 7.

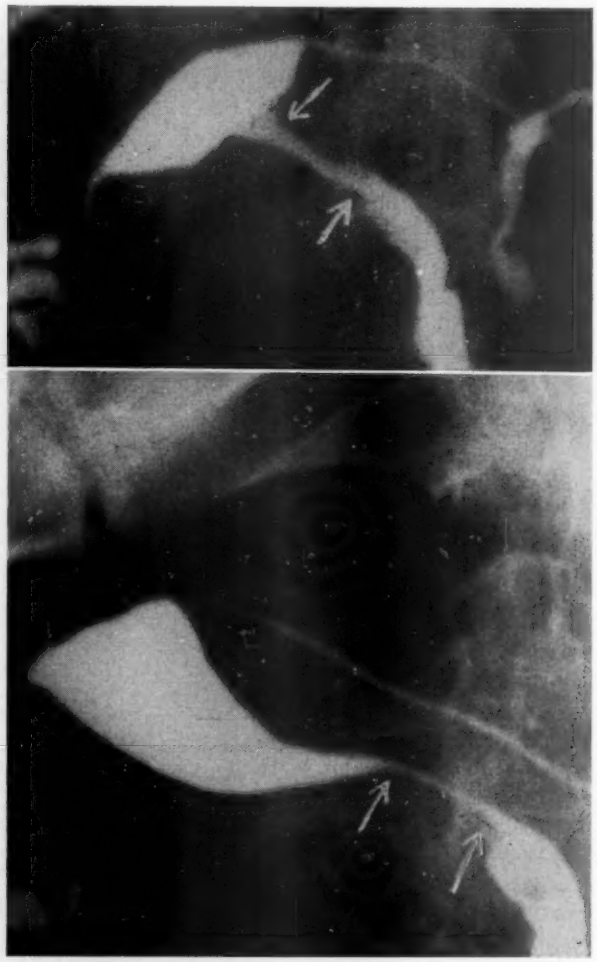

Fig. 8.

Fig. 7.—Case of primary dysmenorrhea examined in the follicular phase of the cycle. Normal cylindrical appearance of the isthmus.

Fig. 8.—Case of primary dysmenorrhea examined in the luteal phase. The isthmus is long and narrow and its sphincters contracted, which is normal for this phase of cycle.

In 5 of the 6 cases of habitual abortion in the second trimester with suggestive history, the typical picture of a dilated incompetent isthmus was shown. Even when examined in the luteal phase of the cycle the isthmic canal appeared very wide and both SIS and IIS were hardly recognizable (Fig. 6). No difference was noted in the appearance of the isthmus in cases of primary and cases of secondary habitual abortion. In one of the cases of habitual abortion the isthmus was seen to be normal but two filling defects were apparent in the contour of the uterine corpus; laparotomy showed the presence of two small submucous myomas which had been missed on clinical examination.

The 12 cases of primary dysmenorrhea investigated by isthmography showed no apparent deviation from the normal when examined in the follicular (Fig. 7) or at the height of the luteal phase (Fig. 8) of the cycle. When, however, examination or re-examination was made one or two days before the period an interesting and original observation was made. Admittedly the number investigated was small, but the difference from the normal appearance was so constant as to be of significance. Here the marked shortening and widening of the isthmus which were always noted in normal cases shortly before the onset of menstruation (Fig. 9) did not occur (Fig. 10). In some cases the

Fig. 9. Fig. 10.

Fig. 11. Fig. 12.

Fig. 9.—Case of hypoplastic acutely anteflexed uterus but painless menstruation. Isthmography on the day before the period shows marked shortening and widening of isthmus and relaxation of both isthmic sphincters.

Fig. 10.—Case of primary dysmenorrhea on the day before the period. The isthmus is short but very narrow. Both isthmic sphincters are contracted.

Fig. 11.—Case of primary dysmenorrhea on the day before the period. SIS is slightly relaxed but lower part of isthmus and IIS remain tightly contracted.

Fig. 12.—Case of primary dysmenorrhea on the day before the period. Isthmus shows multiple constrictions and is markedly irregular.

superior isthmic sphincter was somewhat relaxed but the inferior isthmic sphincter remained tightly closed (Fig. 11). In one case multiple constrictions were seen in the isthmic segment which appeared irregular (Fig. 12). This absence of relaxation of the isthmus in the immediate premenstrual phase which proved so characteristic of primary dysmenorrhea was not detected by Asplund,[3] whose data show that none of his patients with dysmenorrhea was examined in

the 2 days preceding the period. All his patients were examined during the luteal phase and his findings in this phase, like ours, showed no difference between the normal and the dysmenorrheic cases.

Direct Hysterography.—Three of the patients subject to habitual abortion, shown by isthmography to have a wide incompetent isthmus, were subsequently examined by direct hysterography during the luteal phase of the cycle. As soon as Lipiodol was injected into the uterine cavity it leaked through the isthmus and cervix into the vagina before a film could be made. Since this immediate leakage does not occur in normal cases in any phase of the menstrual cycle and least of all in the luteal phase, this may prove a useful test for the diagnosis of incompetence of the isthmus in cases of repeated abortion.

In the 8 cases of primary dysmenorrhea investigated by direct hysterography, no difference from the normal was noted during the follicular (Fig. 13) or the luteal (Fig. 14) phases of the cycle. When examined one or 2 days before the period, however, it was found that shortly after the Lipiodol was injected into the uterine cavity the patient started to complain of severe colicky pains. One developed vomiting and backache similar to what she used to suffer during her menstrual periods. The uterus did not empty itself as rapidly as it normally does at that particular time and some Lipiodol remained inside the uterus 2 to 3 hours after the injection. But, when it came out, it passed, as it did in normal cases, through the isthmus and cervix and not through the tubes. The isthmus appeared, however, much less relaxed than it was in normal cases in this immediate premenstrual phase (Fig. 15).

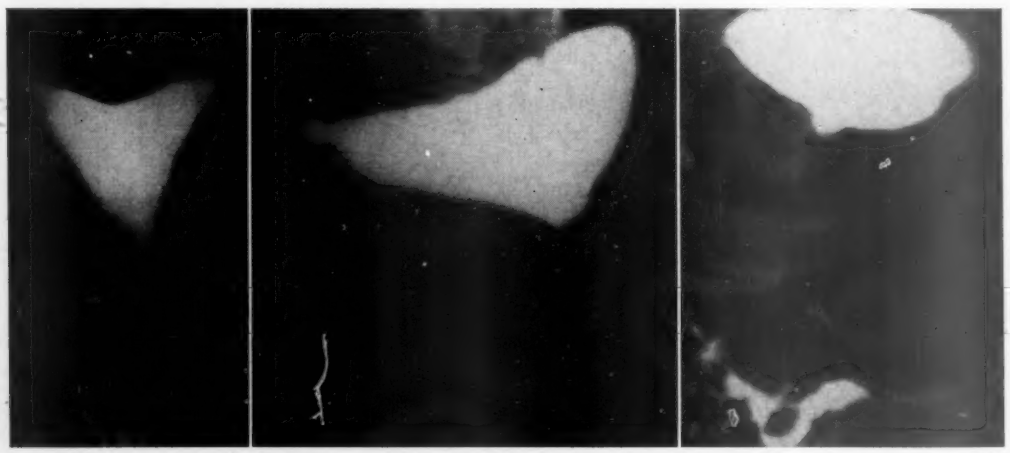

Fig. 13. Fig. 14. Fig. 15.

Fig. 13.—Direct hysterography in a case of primary dysmenorrhea in the follicular phase of the cycle. Film made 2½ hours after injection shows normal appearances (Lipiodol passing through the tubes and through the isthmus and cervix).

Fig. 14.—Direct hysterography in a case of primary dysmenorrhea in the luteal phase. Film made 4 hours after injection shows normal appearances (Lipiodol passing through the tubes but not through the isthmus).

Fig. 15.—Direct hysterography in a case of primary dysmenorrhea in the immediate premenstrual phase. Film made 1½ hours after injection shows Lipiodol still inside the uterus (abnormal). Some Lipiodol has started to pass through the isthmus which appears abnormally narrow for this phase of the cycle.

Comment

The marked constriction of the isthmic canal observed in amenorrheic patients when moderate doses of progestin were administered after estrogen priming confirms the view[3, 15, 16] that the narrowing of the isthmus during the luteal

phase of the normal cycle is caused by the progestin secreted by the corpus luteum. This viewpoint is also supported by our finding that the isthmus remained wide during the second half of anovulatory cycles. The observation that in the absence of estrogen the same dosage of progestin did not change the width of the isthmus is consistent with the view that the action of progestin on the uterine musculature requires adequate priming with estrogen.[17] The curious finding in one patient who received progestin alone that SIS became tightly constricted although the rest of the isthmus and IIS remained unaffected cannot at present be explained although it does show that the two sphincters of the isthmus may act independently and respond differently to hormone action.

We did not investigate the effect of administration of estrogen alone to amenorrheic patients but this had been reported to cause definite isthmic dilatation.[3, 16] Our finding that the isthmus in patients with metropathia was always abnormally wide and its sphincters relaxed seems to lend support to these previous reports. The wide and relaxed appearance of the isthmus both in patients with amenorrhea and postmenopausal patients with very low estrogen function and in those with metropathia with hyperestrinism may seem paradoxical but can be easily explained. In the former cases the widening of the isthmus is due to atrophy of its musculature while in the latter it is due to active dilatation of the isthmic sphincters under the effect of the estrogenic hormone. The relaxation of the isthmus in cases of metropathia explains the painless nature of the bleeding in this condition. It is also the reason why anovular menstruation is always painless.

Habitual Abortion.—One of the important functions of the isthmus is the preservation of pregnancy. Recent studies indicate that the isthmus does not unfold until the twentieth week of pregnancy and that the unfolding noted earlier in some anatomical specimens is artificially produced.[3, 18] Palmer[19] was the first to show that gaping of the isthmus is an important cause of habitual abortion in the second trimester. Lash and Lash[4] described the same entity under the name "incompetence of the internal os." These findings have now been amply confirmed.[6-8, 10] Danforth,[11, 12] however, took exception to this view and insisted that it is the cervix itself, by virtue of its fibrous structure, which constitutes the barrier confining the conceptus in the uterine cavity. We are not here concerned with the controversial question as to whether the cervix is mainly a fibrous structure[20-22] or whether it contains well-defined muscle layers.[23-25] But it is surprising that the same observer who maintained that the cervix is an inert collagenous structure and who so clearly described the fibromuscular junction at the region of the histological internal os[20] should not recognize the importance of the latter structure in the maintenance of pregnancy and should ascribe this function to the inert cervix.[11] The evidence against this viewpoint is overwhelming. The elongation and constriction of the isthmus in early pregnancy[15] which probably persist to the fifth month[3, 18] have already been stressed. When the isthmus later unfolds, there develops in the region of the histological internal os a local accumulation of circular muscle fibers which acts as a compressor,[23, 26] i.e., IIS becomes reinforced. In a careful anatomical study the precocious movement of this circular layer of muscle in a case of habitual abortion at the sixth month of pregnancy was observed.[23] The tone of this muscle is almost unanimously regarded as the essential factor in retaining the ovum.[5, 6, 10, 18, 23, 24, 27] It is very unlikely that the cervix, rendered soft, edematous, and patulous during pregnancy, should be effective in supporting the growing conceptus.[27] The multipara with a badly lacerated cervix may conceive and carry the pregnancy to term although there is no structural support from the cervix.[28] Conization of the cervix is followed by surprisingly little trouble during pregnancy if the electrode does not damage the

fibromuscular junction.[29] Amputation of the cervix as in the Manchester and Sturmdorf operations is not followed by miscarriage[30-33] but if the cervix is removed above the level of the internal os, habitual abortion very often ensues.[9, 10, 33]

Previous radiographic investigations showed that in cases of habitual abortion the actual defect lies at the junction of the corpus with the cervix.[5, 6] The results of these experiments in which balloons or other apparatus were introduced into the isthmus have been fully confirmed by our technique of isthmography which entails no distortion of the isthmic region. Since our findings indicate that in the cases of habitual abortion under discussion the whole isthmic canal is abnormally wide, we believe that the term "gaping of the isthmus" used by Palmer[5] or, better still, "isthmic incompetence" is more accurately descriptive than cervical incompetence, sphincteric incompetence of the cervix[10] or incompetence of the internal os.[4]

In 2 of our cases of habitual abortion due to incompetence of the isthmus there was no history of labor, dilatation, or other trauma and here the isthmic incompetence must have been due to a disturbance of the endocrine-neuromuscular mechanism regulating the isthmus. These were the only 2 cases in our series in which the abortion was repeated after surgical repair of the isthmic region. Palmer[5] had stressed the role of neuromuscular disturbance in some of his cases but Lash and associates[6] minimized the importance of this factor and stated that in virtually all their cases there was an antecedent history of trauma. More recently Hunter, Henry, and Civin[34] re-emphasized the point that some of these cases are not due to trauma. They also found that the results of repair by the Lash method were much less satisfactory in the nontraumatic variety which they called the physiologically incompetent internal os. We think that this name is somewhat paradoxical and suggest the term "dysfunctional incompetence of the isthmus" as a more satisfactory designation of the nontraumatic case.

Primary Dysmenorrhea.—Two thousand years of medical knowledge seem to have added little of basic importance to the original ideas of the ancients[35] on this disease of theories, the etiology of which remains unknown.[36] Too often little differentiation is made between the basic etiological factor and the numerous predisposing conditions. Many of the views on the causation of dysmenorrhea have seemed difficult to correlate with each other or with the observed clinical and experimental facts. Let us now see if the findings of the present investigation can throw some light on this complex problem.

It has been shown that normally shortening and relaxation of the isthmus occur 2 days before the onset of menstruation at the time when the uterine body starts to become strongly active and these changes coincide with the disappearance of pregnanediol from the urine and with the second estrogen peak.[15] In cases of primary dysmenorrhea the isthmus and especially its inferior sphincter remain tightly closed during this critical period, which shows that the basic cause of dysmenorrhea is incoordinated uterine activity. When, in patients with dysmenorrhea, Lipiodol is injected into the uterus by direct hysterography in the immediate premenstrual phase, colicky pains soon occur but the uterus takes a longer time than normal to evacuate itself. When Lipiodol is injected by the same method during the follicular or luteal phase of the cycle the uterus empties itself normally and without pain. This indicates that the uterine contractions themselves are not painful; the pain perceived shortly before and at the beginning of menstruation is the result of the uterus contracting against a sphincter which is abnormally tight. The pain originates in the richly innervated uterine isthmus[37-39] and is due to stretching and incoordinate dilatation of its sphincter system.

In the light of these findings many of the apparently contradictory views on dysmenorrhea can easily be understood and correlated. It is, for example, clear that the menstrual pain is related to uterine contractility,[40-43] although the uterine corpus itself is almost devoid of nervous apparatus.[38] It is conceivable that in cases of dysmenorrhea the uterine contractions are disorganized and dysrhythmic.[40, 41, 44] Since the pain, however, is not due to the uterine contractions themselves or to the ischemia produced thereby, it is not surprising that the intensity of uterine contractions and the intrauterine pressures were found to be just the same in dysmenorrheic as in normal cases.[45, 46] It is likewise understandable that several observers[47, 48] could not demonstrate suppression of the arterial circulation during the pain in dysmenorrhea, while intrauterine pressures higher than the systolic level produced in normal patients by Pituitrin injection were completely painless.[48]

The perplexing but factual observations that dysmenorrhea occurs only in ovulatory cycles,[39, 49-57] although progestin is known to inhibit uterine activity,[17, 58, 59] can also be readily explained. The pain of dysmenorrhea is caused by the uterine corpus, activated by the premenstrual rise of estrogen and fall of progestin, acting against a sphincter which failed to relax after having contracted under progestin effect. This view is in agreement with the assumption[36, 57, 60] that dysmenorrhea may be caused by some sort of imbalance between estrogen and progestin. The dysmenorrheic career does not, as a rule, start until some time after puberty.[60, 61] Since the early periods are usually anovulatory the isthmus remains relaxed in the second half of the cycle and during menstruation which is therefore painless.

The cure of dysmenorrhea after labor or cervical dilatation is obviously due to stretching of the isthmic sphincters. Cervical dilatation is more effective if it is continued until all resistance at the internal os is overcome,[62, 63] or if a stem pessary[63-65] or a metranoikter[66] is used. If recurrence of pain occurs it is due to regeneration of the muscle fibers.[62] New color is thus given to the obstruction theory[67]; clearly what is important is not organic cervical obstruction but functional obstruction at the isthmic sphincters. It is therefore not surprising that most women with a pinhole os or a cervical stricture have no dysmenorrhea[36, 68] and that a uterine sound can as easily be passed in the dysmenorrheic patient as in the normal one.[36] It is conceivable that in the sexually immature individual with an ill-developed uterus the endocrine-neuromuscular regulation of the isthmus may not always be efficient; hence the common[13, 57, 69-71] but far from constant[62, 72] finding of hypoplasia in cases of dysmenorrhea.

There is evidence that the autonomic nerve supply of the uterus, which is almost confined to the region of the isthmus,[37, 38] is involved in regulating the tone of the isthmic sphincters,[5, 73] which explains the finding of degenerative or inflammatory changes in the autonomic system in the vast majority of dysmenorrheic patients,[35, 74-78] the almost constant improvement after presacral neurectomy,[78-86] and the frequency of association of other manifestations of autonomic disturbance with the dysmenorrhea syndrome.[62, 87]

Ordinary antispasmodics very often prove unsuccessful in treatment, apparently because they fail to produce relaxation of the isthmus. In the past few years, however, certain relaxants have been discovered and are being tried, which seem to produce dramatic results in cases of primary dysmenorrhea.[88-95] Some of these act directly on the smooth muscle while others act at the neuromuscular junction. Most interesting in this respect is the recent report by Hunter, Henry, and Heinicke[95] on the spectacular effect of the relaxant enzymes papain and bromelain in cases of primary dysmenorrhea. These authors

demonstrated radiographically that these enzymes actually cause very marked relaxation of the sphincter in the region of the internal os, which is followed by immediate relief of the dysmenorrheic pains.

It is possible that psychosomatic disturbances may impair the coordinated function of the uterine isthmus by increasing the irritability of the uterine neuromuscular system.[87] Yet there is strong evidence that the psychogenic factor cannot be the primary cause of dysmenorrhea.[36, 71, 96-98] Susceptible individuals, however, tend to react to pain abnormally and a vicious circle may be established.[99-102] Even the mechanism of action of such rare predisposing factors as allergy[103, 104] can be explained. This would presumably act by causing spasm of the isthmic sphincters similar to the bronchiolar spasm in asthmatic patients.

Conclusions

The sphincter mechanism of the isthmus is susceptible to the action of the ovarian steroids. The administration of progestin to amenorrheic patients after estrogen priming results in marked constriction of the isthmus. In metropathia hemorrhagica and in anovular menstruation the dilatation of the isthmus is due to the unopposed estrogen effect. This is why the bleeding in such cases is always painless.

Certain cases of habitual abortion in the middle 3 months of pregnancy are due to incompetence of the isthmus. This can be demonstrated radiographically by the methods of isthmography and direct hysterography, best carried out during the luteal phase of the cycle. The incompetence of the isthmus may be traumatic or dysfunctional. The distinction is important since the results of surgical repair (isthmorrhaphy) are much less satisfactory in the dysfunctional cases. It remains for the future to discover an objective means of differentiation between these two varieties and to find out an effective therapy for dysfunctional incompetence.

The basic abnormality in primary dysmenorrhea is failure of normal relaxation of the isthmus in the immediate premenstrual period and at the beginning of menstruation. This may be due to a temporary hormone imbalance or to abnormal response of the isthmus to normal endocrine influences. No difference in the estrogen-progestin equilibrium in the immediate premenstrual phase in normal and dysmenorrheic patients has yet been demonstrated. But the final answer to this question must come from laboratories equipped with modern facilities for blood hormone assays. On the other hand, there is evidence that the hormonal control of the isthmus is mediated through the autonomic nervous system and that this system is implicated in primary dysmenorrhea. Further investigation is clearly indicated to solve this problem and to find a way to rational treatment. The only two therapeutic methods at present uniformly successful, namely, suppression of ovulation and presacral neurectomy, are far from satisfactory, the former being too unphysiological and the latter too drastic. The role of the psychogenic factor should not be undervalued. But clear distinction must be made, if we are finally to solve the riddle of primary dysmenorrhea, between the basic etiology and the predisposing or contributing factors.

Summary

1. The results of examination of a group of abnormal cases by the methods of isthmography and direct hysterography are discussed.

2. Some cases of habitual abortion in the second trimester of pregnancy are due to traumatic or dysfunctional incompetence of the isthmus. Dysfunctional incompetence is not cured by conventional isthmorrhaphy.

3. The basic abnormality in primary dysmenorrhea has been demonstrated. The cause underlying this abnormality remains to be found.

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FERTILITY CONTROL WITH ORAL MEDICATION*

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FOLLOWING the demonstration of the ovulation-inhibiting effectiveness of several oral progestational 19-nor steroids in animals,[1-3] and in a group of selected patients,[1, 4-7] a field trial in Puerto Rico was undertaken, with the use of one of these compounds. Norethynodrel [Compound II—17α-ethinyl-5(10)-estraeneolone—of our previous studies] was chosen since in animal experiments it appeared to be somewhat more potent than the others in suppressing ovulation. It also gave some indication of preventing fertilization in rats.[3] Moreover, in low dosages, combined with a subeffective estrogen, it regulated menstrual cycles when given cyclically.[7-9]

The most effective estrogen supplement appeared to be the 3-methyl ether of ethinyl estradiol. In 1,467 of the cycles studied in this investigation, the subjects received tablets each containing 10 mg. of norethynodrel and 0.22 mg. of the ethinyl estradiol 3-methyl ether, or, in a very few instances, 0.23 mg. In the remaining 390 cycles reported, the estrogen supplement was somewhat lower, i.e., 0.08 mg. in 157 cycles, 0.15 mg. in 61 cycles, and 0.18 mg. in 172 cycles.†

The procedures employed in assembling subjects, the instructions given, the regime of medication, the problems encountered, and some of the results of the first 8 months of the Puerto Rican study have been described previously by Rice-Wray[10] and by Pincus and his associates.[7, 9] This paper extends the data to Aug. 31, 1957, i.e., to include a total of 16 months of investigation.

Subjects and Methods

Since the details of the procedures used with the married Puerto Rican subjects have been published,[10] it suffices here to state them briefly.

Considered in this report are 1,857‡ cycles of 265 Puerto Rican wives "from the low income population living in a housing development project in a

*The investigation described in this paper has been aided by a research grant from G. D. Searle & Company which, with the medication used, was obtained through the kindness of Dr. A. L. Raymond and Dr. I. C. Winter.

†Tablets containing 10 mg. of norethynodrel and 0.15 mg. of 3-methyl ether of ethinyl estradiol constitute the trademarked product Enovid, G. D. Searle & Company.

‡A total of 1,857 cycles was studied in this investigation. These comprised 1,712 cycles for which we have data on lengths (Table I), plus 118 for which such data were not available, plus an additional 27 in the 19 women who became pregnant.

TABLE I. DISTRIBUTION OF LENGTHS OF MENSTRUAL CYCLES AS INFLUENCED BY DISCONTINUITY OF MEDICATION
(265 Women: 1,712 Cycles)

TOTAL NO. OF CYCLES	NO. OF TABLETS MISSED		LENGTH OF CYCLE											
			7-12	13-18	19-23	24-25	26	27	28	29	30	31	32	33-36	37-48
1,279	(A) 0	No.	6	13	26	90	163	322	276	130	67	67	65	33	21
		%	0.5	1.0	2.0	7.0	12.7	25.2	21.6	10.2	5.2	5.2	5.1	2.6	1.6
282	(B) 1-5	No.	19	45	55	7	4	7	8	16	19	32	32	29	9
		%	6.7	16.0	19.5	2.5	1.4	2.5	2.8	5.7	6.7	11.3	11.3	10.3	3.2
151	(C) 6-19	No.	1	4	10	2	1	10	3	3	11	9	20	53	24
		%	0.7	2.6	6.6	1.3	0.7	6.6	2.0	2.0	7.3	6.0	13.2	35.1	15.9

slum clearance area."[10] The ages of 262 were known. They extended from 16 to 44 years with a median of 27.4* Prior to the beginning of medication, the incidence of pregnancy in these women had been 63 per 100 years of marriage (i.e., 0.625 ± 0.0135 per year) in spite of some use of contraceptive measures.

Every woman was given one or two vials, each containing twenty 10 mg. tablets of the drug, with instructions to take one tablet a day, beginning on day 5 of the menstrual cycle, until one vial of 20 tablets was consumed, i.e., through day 24 of the cycle. If a tablet was not taken on any given day, the subject was instructed to proceed with the one-a-day regime nonetheless until all 20 tablets were used.

A schedule of visits by a trained social worker was arranged so that in every medication cycle each subject was seen shortly after she should have taken the last tablet. Initially only one vial was distributed to each woman. This was replaced on the social worker's visit. Since, in a number of instances, the housewives were not at home when she called, it was decided, after a few months, to leave two vials with each subject so that the continuity of the regime of medication (day 5 through day 24) might not be broken. Visits on the same schedule were nonetheless made, and missed interviews were followed by another visit within one to two weeks.

At each consultation, information was elicited concerning the length of the menstrual cycle, the occurrence of side effects, the frequency of coitus, and the number of missed tablets. A rough check, in some instances, on the number of tablets omitted was made by counting those remaining in the vial. As subjects discontinued the study, replacements were sought, so that an average monthly load of approximately 130 women was maintained.

In the course of the investigation, many of the participants came to the office of the Family Planning Association, or of an affiliated physician, for pelvic examination. At this time, an endometrial biopsy was taken and blood drawn for hemoglobin determinations, bleeding time, and clotting time. A limited number of individuals also furnished urine for assays of certain steroids.

Results

Lengths of Menstrual Cycles.—Adequate information for analytical purposes was obtained from 1,712 cycles of 265 women. In Table I are presented the data on lengths of menstrual cycles, arranged according to the number of days that tablets were omitted.

It is shown that out of a total of 1,712 medication cycles, 1,279 (A) were reported with no omissions of medication, 282 (B), with one to five tablets missed, and 151 (C), with six to nineteen tablets unused. The mean lengths of cycles in the three groups are: (A) 27.86 ± 0.515; (B) 25.34 ± 1.529; and (C) 32.01 ± 0.923 days, respectively. Statistically significant are differences between the means for A and C, as well as between those for B and C, but not between A and B, because of the large variability in the data for B.

Table I presents the frequency distribution of the different cycle lengths. It is apparent that in the patients who missed no tablets, this is monomodal, with a peak at 27 days. In contrast, where one to five tablets were omitted, a clear

*The age distribution was as follows:

AGE IN YEARS	NO. OF WOMEN
16 to 19	20
20 to 24	77
25 to 29	72
30 to 34	50
35 to 39	40
40 to 44	3
	262

bimodal distribution is seen, with peaks at 19 to 23 days and at 31 to 32 days. When more than five tablets were unused, we observe a minor mode at 19 to 23 days, with a major peak at 33 to 36 days. The degree of variability is expressed by the standard deviation (S) of the distribution, which is highest in B (25.67 ± 1.08), lowest in C (11.37 ± 0.65), and intermediate in A (18.44 ± 0.36). Each of the S's differs significantly from the two others.

In seeking explanations for the nature of the distributions of cycle lengths in each case, it should be recalled that cessation of medication with this compound was found in previous studies[5, 7] to be followed in most cases by withdrawal bleeding within 4 days.

It can be seen from Table I, however, that among 1,279 cycles of the Puerto Rican housewives who took medication from day 5 through day 24, there were 981 cycles in which the flow began at intervals from 3 to 24 days after the last pill was taken. There were, among these, 8 cycles which were of 41 to 48 days' duration.* Postmedication flow in these 8 did not occur until 17 to 24 days after the consumption of the last tablet. There was no constancy in position of the long cycles among the others. Each of these women had but one such lengthened cycle, none having exhibited this phenomenon in any other cycle in which no pills were missed.

The ages of the 8 women ranged from 21 to 38 years (mean, 29.4 ± 5.4; median, 29.5 ± 8.5). Thus age was not a factor. Unfortunately, we have no accurate knowledge of pretreatment cycles. Nor in any of the 8 cycles was a biopsy obtained after medication was completed. We do have one endometrial specimen, however, taken after medication in a 38 day cycle of one of these women. This was obtained on the ninth day after 20 daily increments of 10 mg. of the medication, i.e., on the thirty-third day of the cycle. Flow began on the thirty-ninth day.

Microscopic examination of this tissue showed the stroma to be made up of widely separated cells the nuclei of which were not dissimilar to, unless slightly smaller than, predecidual nuclei. In one small area, there was the ordinary stainless edema commonly seen in early progestational endometrium. Elsewhere, with their attenuated fibrinous cytoplasm, the stromal cells formed a reticulum of strands and vacuoles.

The glands were sparse, small, straight, and lined by pseudocuboidal epithelium in which there was no mitotic activity. The venules were not remarkable in number, although all but two larger ones were filled with blood. No characteristic spiral arterioles could be identified in the biopsy fragments.

We are not prepared to explain the peculiarly long latency preceding withdrawal flow in these women. In the single biopsy available, there was no suggestion of involution to a pretreatment condition; but also there was neither evidence of persistent progestational action, nor of proliferation. Except for the reticulation of the formerly contiguous pseudodecidual stroma cells, the endometrium seemed to be in a suspended state and gave us no indication of what transpired in the ovary or hypophysis to account for the delay in catamenia.

The integrity of the endometrium was not always maintained by the compound. In a previous communication,[7] it was reported that in about 8 per cent of women who received estrogen-supplemented norethynodrel, a breakthrough bleeding occurred before the nineteenth day of medication. In group A of the present series (where no pills were omitted), the distribution of cycle lengths simulates that seen in normally menstruating women as closely as would appear possible by artificial control. To illustrate this, we present in Fig. 1 our data and, for comparison, those of Haman[11] on 2,410 menstrual cycles of 150 normal

*Two recently disclosed cycles, not among the 1,279 under discussion, were even 57 and 58 days long, although no pills were missed.

American married women, along with the statistical constants for each set of observations. It may be seen that in the two tabulations there is no significant difference in the mean length of cycles. Haman's curve on the normal American housewife shows a broader, flatter distribution, however. This implies that medication with norethynodrel tends to narrow the range of cycle lengths.

The 19 to 23 day mode (19.5 per cent) for group B in which one to five tablets were omitted suggests the frequent occurrence of either withdrawal or breakthrough bleeding. Since in Haman's group of normal women the frequency of cycles of 23 days or less was 5.2 per cent, and in group A of our series it was even lower (only 3.5 per cent), it appears that the higher incidence (42.2 per cent) of such short cycles in B was due chiefly to withdrawal bleeding; i.e., the omission of medication occurred sufficiently early in the cycle to precipitate flow.

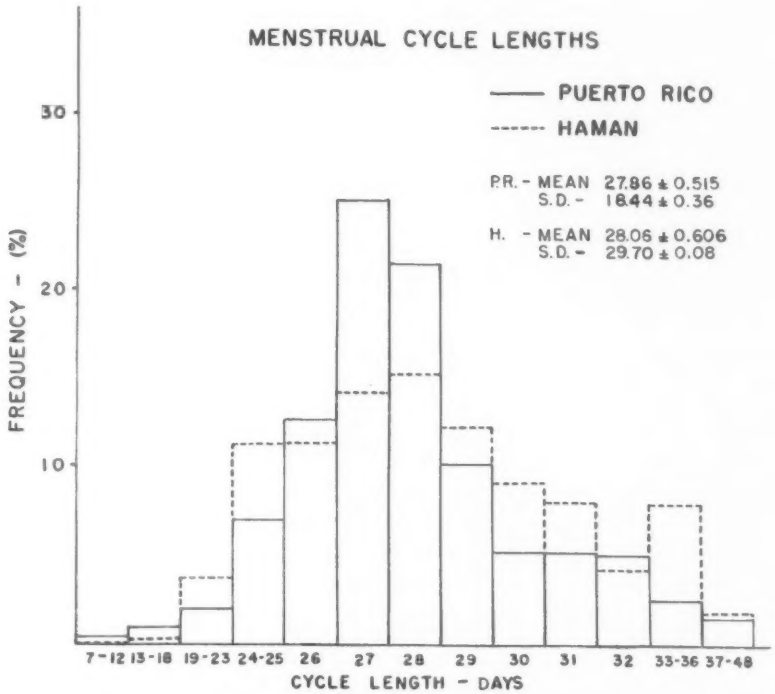

Fig. 1.—Comparison of lengths of menstrual cycles of Puerto Rican women during medication versus those of untreated American women (Haman[11]).

The second mode of B at 31 to 32 days represents approximately 40 per cent of the medication cycles in which, despite an occasional missed tablet, withdrawal bleeding did not occur. These were presumably cases in which the sustenance of the endometrium from the medication was adequate to compensate for the temporary omission of one to five pills. The length of the cycle was therefore increased until the ingestion of the last tablet was followed by the usual withdrawal flow.

In group C, where 6 to 19 tablets were omitted, the minor mode at days 19 to 23 presumably represents the few women with withdrawal bleeding caused by skipping tablets early in the cycle, whereas the 33 to 36 day mode again reflects the delay due to the longer time necessary for the consumption of all 20 tablets. In this connection, it is also possible that women with longer cycles typify those whose endometrial response thresholds to the drug are so low

that sustainment might be expected to occur despite missed pills. Lacking data as to the exact days when tablets were unused, we cannot be more specific in regard to this possibility.

The foregoing observations indicate: (a) that, if the regime of day 5 through day 24 is followed strictly, a normal frequency of menstrual cycle lengths may be expected; (b) that the skipping of days may result in either a shortened cycle due to withdrawal bleeding, or in a lengthened cycle, owing to the extension of medication. Actually, in view of the ability of this compound to prevent menstrual bleeding as long as it is taken,[12] a cycle of any desired length could presumably be produced. We had chosen our standard day 5 through day 24 regime in the expectation that "normal" cycle lengths would occur.

Inhibition of Ovulation.—Our belief, on the basis of previous studies, that this compound is ovulation inhibiting was strengthened in these subjects, who continued their usual coital habits, by the inverse correlation between the incidence of pregnancy and the constancy of medication.

In the 1,279 cycles during which the regime of treatment was meticulously followed, there was not a single pregnancy. On the other hand, in the 282 cycles wherein one to five tablets were omitted, conception occurred in 2 instances; while in those cycles (151) where six or more tablets were unused, there were 3 pregnancies.

As has already been noted previously, the premedication pregnancy rate in these women was 0.625 ± 0.0135 pregnancies per year of marriage. In those who faithfully followed the schedule of medication with no omissions, this rate was 0, a reduction of 100 per cent; among individuals who missed one to five tablets the rate was 0.092, while among those who omitted six or more tablets it was 0.259. The rate for the entire group of medicated subjects was 0.038, representing a reduction of 93.9 per cent from the mean premedication pregnancy value.

In spite of what is, in all probability, an inhibition of ovulation during the cycles in which the regime of medication was meticulously followed, the fact that 2 women conceived during cycles in which not more than five tablets were missed suggests no deleterious effect on the ovary from this drug. Further evidence that it does the ovary no permanent harm is given by the occurrence of pregnancies in 14 women after cessation of medication which had been taken from one cycle to as many as 17 cycles (in one case).

Endometrial Biopsies.—In the course of the medication cycles, intermittent endometrial biopsies were obtained from some of these subjects. Such fragments, if taken from high on the anterior or posterior wall, ordinarily give a true picture of the over-all condition of the responsive portions of the endometrium; but, it must be noted, they may show only an isolated, atypical condition. Thus, when we use endometrial biopsies to detect the estrogenic or progestational potency of an experimental hormone, we must realize the limitations of the method, hence the possible inexactness of the conclusions.

Preliminary studies of Hitschmann and Adler[13] and of Schröder,[14] extended by O'Leary,[15] Bartelmez,[16] our own group,[17-19] and others, have established general criteria by which we judge the potency of an experimental estrogen or progestin against the respective standard action of a familiar estrogen or progesterone.

As we have noted previously,[5] the endometrium appears to be somewhat thinner than one might expect in women of these ages. The histology of the endometrial specimen varies with the duration of medication.

Norethynodrel is a potent progestin by conventional endometrial standards, and, by virtue of its supplementation with the 3-methyl ether of ethinyl estradiol, the combined product (Enovid) has at least temporarily some of the effects of estrone. When given from days 5 through 24 of a menstrual cycle to women who habitually ovulate, its cytologic effects on the endometrium mimic mucosal changes seen with normal ovulation, but with some significant differences (Fig. 2).

In the first place, with medication as described, at a time when we know that in all probability there is no luteinized ovarian follicle and no gonadotrophic influence which would evolve a corpus luteum from such a follicle (i.e., the ninth day of the cycle for example), we see the normal effect on glands of a 4-day-old corpus luteum (Fig. 2, 18 day normal ovulatory cycle). Since biologists have found no gonadotrophic action, tumultuous or otherwise, in these compounds, we must conclude that the morphologic changes reflect only the *direct* influence of the ingested material on the endometrium, and do not indicate premature ovulation on, or soon after, the day treatment was begun, i.e., day 5 of the cycle.

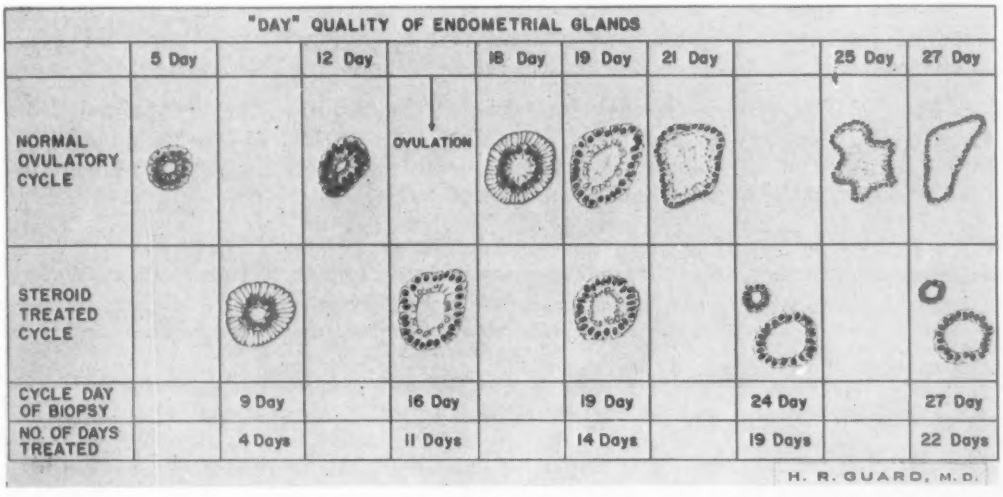

Fig. 2.—Time differential in development of endometrial glandular epithelium in normal and medicated women.

A second aspect of the dissimilarity between endometrium subject to the 19-nor steroids and that of the untreated normal cycle is the short duration of this immediate, so-called secretory response in the glands. With continued medication, it rarely progresses to full, typical secretion by glandular epithelium. Nor, as treatment progresses, do the glands themselves increase in size or change in shape to resemble those subject to a 5, or 6, or 7 day corpus luteum (nineteenth, twentieth, or twenty-first day of the schematic normal cycle).

Instead, in their shapes and in their epithelial structure the glands give the appearance of gradual regression, not to the condition typical of late proliferation but to a condition suggestive of the fifth postovulatory day (nineteenth day of the normal cycle), when actual discharge of vacuole material is beginning. Although the glands themselves remain of proliferative caliber, they are straight or only slightly ribboned. To escape necessity of description, we have called them 19 day glands, because pseudostratification has passed and vacuoles are above the nuclei. After 18 days of treatment, biopsy on the twenty-forth day of the cycle reveals the lumina to be narrower and the epithelium pseudocuboidal, as in the very early proliferative phase. After 3 weeks of medication,

there may be slight variation in caliber of the glands, but most are small and lined by flat cuboidal cells. They closely resemble glands characteristic of the fifth day of a normal cycle.

A third difference between treated and nontreated endometria is that the generalized edema of the functional layer, typical of the week-old corpus luteum effect, appears in the first few days of treatment and, with continued medication, persists with gradual decline until the twenty-first day; whereas, with normal ovulation, the edema begins to subside only *after* the twenty-first day.

Fourth, with treatment starting on day 5, the predecidual cytoplasmic enlargement of stromal cells appears 7 days later, on the twelfth day of the cycle, and progresses rapidly. As early as the twenty-first day of the cycle the stroma closely resembles that of the untreated cycle day 27 (thirteenth postovulatory day). By the twenty-second day of treatment, the stroma so closely simulates that of early pregnancy as to mislead the unwary.

Also significant is the fact that the endometrial diagnosis does not vary with the number of previous cycles of drug administration. A sample taken at a given time in an early medication cycle is indistinguishable from one taken at the same time in a subsequent cycle of treatment. This suggests that the material imposes a sequence of endometrial change which is repeated cycle after cycle.

Steroid Excretion.—Twenty-four hour urine samples were obtained from 42 subjects, 10 of whom had withdrawn from the project at least 2 months before the inception of the steroid excretion study. These 10 served as controls for the 32 on medication when urine was collected.

TABLE II. EFFECTS OF MEDICATION ON THE URINARY EXCRETION OF CREATININE (CR), 17-KETOSTEROIDS (17 KS), AND 17-HYDROXYCORTICOSTEROIDS (PS) IN 42 PUERTO RICAN WOMEN (32 During Medication: 10 Controls)

NO. OF CYCLES ON MEDICATION	NO. OF SUBJECTS	MEDIAN AGE (YEARS)	CR (GM. PER 24 HOURS)	17 KS (MG. PER 24 HOURS)	PS* (MG. PER 24 HOURS)
"Withdrawn" (control)	10	28	1.20 ± 0.027	4.24 ± 0.74	3.45 ± 0.41
1-4	17	27	1.22 ± 0.113	2.92 ± 0.40	2.00 ± 0.24
5-10	15	27	1.13 ± 0.113	2.76 ± 0.50	2.29 ± 0.38
1-10	32	27	1.17 ± 0.078	2.85 ± 0.31	2.14 ± 0.22

*Underlined values differ significantly from values of the "withdrawn" group.

In Table II are listed the mean data obtained on urinary output of creatinine,* 17-ketosteroids (determined on an aliquot by the method of Pincus[20]), and 17-OH-corticosteroids (determined on an aliquot by a modification of the Porter-Silber[21] method).

Although the mean 17-ketosteroid excretion (KS) of 2.85 mg. per 24 hours in the medicated group (1 to 10 cycles) is 33 per cent less than the value for the control group, it is not quite significant statistically. On the other hand, the 38 per cent difference between output values of 17-OH-corticosteroids (PS) in control and medicated groups (1 to 10 cycles) is highly significant statistically ($p<0.001$). These data suggest an inhibition of excretion of adrenocorticosteroids with the establishment of a constant lowered output level during medication. In this connection, it should be pointed out that in a study of 7 psychotic women on whom similar determinations were made during the same regime of medication, each subject having served as her own

*In view of the known constancy of creatinine excretion, determinations were used merely as a check on the completeness of the 24 hour urine specimens submitted for analysis.

control prior to taking the drug, the decline in mean output of 17-OH-corticosteroids was only 16 per cent, and of 17-ketosteroids only 18 per cent.[9] There is therefore some doubt as to whether the 10 "withdrawn" subjects of the present study serve as adequate controls to the subjects on medication. A small but definite decrease in excretion of 17-ketosteroids has been reported previously in several series of observations.[6, 7] This lowered output was, however, still within the normal range, and no symptomatic evidence of decreased adrenal function was noted.

Blood Studies.—Routine bleeding time, clotting time, and hemoglobin values were determined, at indefinite intervals, on 39 of the subjects of this study during medication, as well as on 10 women after discontinuance of the treatment 3 to 8 months previously. To serve as controls, 26 women were tested who were untreated patients in the Family Planning Association Clinic.

Cases of medication for 1 to 12 cycles are represented in this blood study, but since no difference in values was seen between those on short-term and those on long-term medication, we averaged all the data for patients taking the drug.

TABLE III. THE EFFECT OF MEDICATION ON BLOOD OF PUERTO RICAN WOMEN
(49 Medicated: 26 Controls)

SUBJECTS	NO.	BLEEDING TIME* (SECONDS)	CLOTTING TIME* (SECONDS)	HEMOGLOBIN	
				%	GM.
Control	26	145.9 ± 8.21	278.8 ± 10.7	75.4 ± 1.09	11.77 ± 0.21
Medicated	39	116.8 ± 6.31	261.5 ± 7.02	73.8 ± 1.02	12.04 ± 0.17
After medication	10	103.4 ± 12.4	223.9 ± 15.5	75.2 ± 2.51	12.75 ± 0.4

*Underlined values differ significantly from the control values.

As shown in Table III, the average bleeding time, both during and after medication, is significantly shorter than in the controls. It also appears that the clotting time in the postmedication subjects is significantly less than in either the control or the medicated group. No significant differences in hemoglobin content are seen among the three groups, however. While there is a tendency toward higher hemoglobin in the medicated and postmedicated subjects as compared to the controls, this difference is not significant.

Side Effects.—Some of the women on this medication occasionally exhibited troublesome symptoms which, in a number of instances, led them to discontinue the tablets. Reactions which may be attributable to the compound are breast tenderness, nausea, dizziness, vomiting, and pelvic pain. We have recently analyzed the incidence of such reactions in two groups of patients who received norethynodrel on the day 5 through day 24 regime over periods of a few months.[7] Two findings were outstanding: (a) the incidence of untoward effects was very low with norethynodrel itself, but increased when estrogen was added as a supplement, and (b) the frequency of such reactions was highest during the first cycle of medication and was significantly lower in later cycles. In the Puerto Rican series reported here, we studied the incidence of reactions in 390 cycles of patients receiving norethynodrel with supplements of 0.08 mg. (157 cycles), 0.15 mg. (61 cycles), and 0.18 mg. (172 cycles) of the 3-methyl ether of ethinyl estradiol per 10 mg. of norethynodrel, instead of the usual 0.22 mg. There was no difference in the incidence of reactions in the three groups, although a significant increase of early bleeding occurred at 0.08 mg. of the estrogen supplement. It appears, therefore, that the threshold estrogen dose for these reactions is lower than that for adequate endometrial support.

Since norethynodrel, as administered to these Puerto Rican subjects, has had estrogen supplementation varying from 0.08 mg. to 0.23 mg. per 10 mg. of norethynodrel (in the great majority of cycles, the supplement was 0.22 mg.), we may consider that a suprathreshold level for reaction stimulation has been employed. Let us examine the consequences.

TABLE IV. PERCENTAGE OF PUERTO RICAN WOMEN WHO DISCONTINUED MEDICATION AFTER ONE OR MORE CYCLES BECAUSE OF REACTIONS

CYCLE NUMBER	NUMBER OF SUBJECTS	LEFT BECAUSE OF REACTIONS		SURVIVORS PER 1,000 WHO STARTED
		NO.	%	
1	265	5	1.9	981
2	234	5	2.1	960
3	208	4	1.9	942
4	186	5	2.7	917
5	163	8	4.9	872
6	137	1	0.7	866
7	119	3	2.5	844
8	101	5	4.9	801
9	83	0	0.0	801
10	76	1	1.3	791
11	64	1	1.6	778
12	57	1	1.8	764
13	52	2	3.8	735
14	45	0	0.0	735
15	41	0	0.0	735
16	32	0	0.0	735
17	22	0	0.0	735
18	18	0	0.0	735
19	8	0	0.0	735
20	2	0	0.0	735
21	1	0	0.0	735

In Table IV are presented the data on the number of patients who withdrew from the project because of side effects. From the percentages of women who stopped medication, we have calculated the crude survival rates per 1,000 starting. These survival data are charted in Fig. 3. From the shape of this curve, it is clear that the rate of discontinuance of medication caused by untoward reactions declines with time in such a manner that 13.4 per cent will have left after 6 cycles of medication, 23.6 per cent after 12 cycles, and 26.5 per cent after 18 cycles. The departure rates in these 6 cycle increments are thus 13.4, 10.2, and 2.9 per cent, respectively. In the initial 1½ years, therefore, approximately 27 per cent of the subjects stopped medication because of troublesome symptoms, while thereafter the loss from this cause was negligible. This remainder represents either subjects who have become habituated so that the reactions are not troublesome to them, or women who have high thresholds of reaction stimulation. With the information available, we cannot at present decide just which explanation applies.

Because of these complaints, a special observation period of 3 months was instituted, during which the incidence of reactions was noted, and to a number of the patients tablets of a magnesium aluminum glycinate antacid were dispensed. Fifty-two women in all had reported reactions in 502 medication cycles. Of 39 of these patients, who took from 1 to 10 antacid tablets, 32 reported disappearance of their symptoms: an apparent "cure rate" of 82 per cent. Of the remaining 13 women subject to reactions, who did not take the antacid, however, 6 observed a spontaneous disappearance of symptoms, while 7 did not, suggesting a spontaneous "cure rate" of 46 per cent, or an incidence of 54 per cent of continued reactions. We would therefore expect that 46 per cent of the group of 39 who took the antacid (or 18) would have shown spontaneous

remission. This leaves 21 who would be expected to show continued untoward effects, and since only 7 did so, the true "cure rate" by the use of antacid tablets is 67 per cent.

Regardless of these considerations, if our data be taken literally, we would expect, by administering antacid, to inhibit reactions in 82 per cent of the reactors, presumably reducing by this percentage the number of women who discontinue medication. Further tests of the control of untoward effects are in progress.

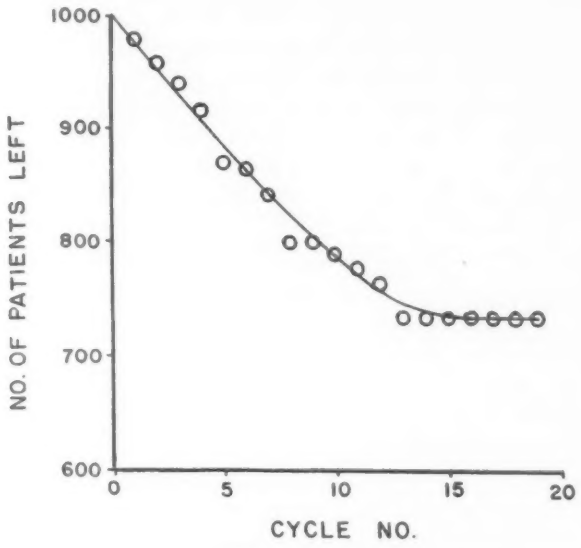

Fig. 3.—Rate of discontinuing medication because of reactions (expressed as per 1,000 women starting medication).

Fertility Control.—As of Aug. 31, 1957, there were 141 patients continuing on medication, while 123 had, for various reasons,* discontinued it. In Table V are listed the reasons for dropping out and the number of women in each of the categories.

From the point of view of contraceptive practice, the subjects in categories a, e, d, i, j, and k, i.e., 64 of the 123,† are susceptible to conception in the test population. Some of these 64 have adopted other means of contraception.

The 14 patients listed as "pregnant with disuse" (e) consist of 10 who failed to take medication through carelessness and 4 who discontinued because of troublesome symptoms. Because the latter 4 are included under "pregnant with disuse," they do not contribute to the 37 listed under "reactions." The 14 in group e are 9 who became pregnant in the first cycle after they stopped medication, and 5 others who, having failed to adopt any other means of contraception, conceived within 2 to 5 months after discontinuation.

Those listed as "pregnant during use" (d) are the 5 already mentioned who missed 3 to 17 tablets.

*It should be noted that 56 other subjects, who volunteered to take part in the project but who did not continue, are not included in this discussion. Twelve of them were pregnant before they began the medication, while, for the remaining 44, adequate information is not available, either because they moved and could not be traced, lived too far away for visits, or apparently failed even to start medication. Some "bootleg" sales of the drug were traced to the latter group.

†The reason why 54 of the remaining women, i.e., groups b, e, f, g, h, discontinued medication are obvious (Table V). The members of group l included 1 menopausal woman, 1 with an "uncooperative attitude," and 3 prostitutes.

Although all of these pregnancies are obviously attributable to failure of the subject, rather than of the method, we have an over-all incidence of 19 pregnancies in 1,857 cycles, or 143 marriage years, an incidence of 13 pregnancies per 100 years. When this figure of 13 is compared with the premedication pregnancy rate of these same women (63 per 100 marriage years), we find a reduction of 80 per cent in the pregnancy rate during the use of this compound. It is of interest, also, to compare our figure of 13 with pregnancy rates reported in a previous study of Puerto Rican women who used other types of contraceptives, i.e., 29 pregnancies per 100 exposure years with diaphragm and jelly, and 33 with foam powder and sponge.[22]

Finally, to enable us to compare our figures with the pregnancy rate when no contraceptive measures were used, Dr. Clarence J. Gamble[23] has furnished us with data on pregnancy rates based on his observations on 1,443 patient years with Puerto Rican couples. For all ages "under 20" to 44, the rate was 76 pregnancies per 100 couples per year. Correcting for the age distribution of our subjects, we would expect 67 pregnancies per 100 years of marriage. Our observed incidence of 13 per 100 years is 19 per cent of this, suggesting an "effective" reduction in the pregnancy rate of 81 per cent.

TABLE V. REASONS FOR DISCONTINUING MEDICATION
(123 Puerto Rican Women)

	NO.	% OF TOTAL DISCONTINUING	% OF TOTAL SUBJECTS
(a) Reactions	37	30.1	14.0
(b) Moved or too distant	19	15.4	7.0
(c) Pregnant with disuse	14*	11.4	5.5
(d) Pregnant during use	5	4.1	2.0
(e) Sterilized	11	8.9	4.0
(f) Separated from husband	10	8.1	4.0
(g) Husband sterilized	7	5.7	2.5
(h) Unrelated illness	7	5.7	2.5
(i) Husband against practice	4	3.3	1.5
(j) No interest	3	2.4	1.0
(k) Religion	1	0.8	0.5
(l) Miscellaneous causes	5	4.1	2.0
Total	123	100.0	46.5

*Four of these stopped medication because of reactions.

Summary

As the outstanding findings resulting from this investigation, we may state the following:

1. Length of the Menstrual Cycle.—

A. The ingestion of 10 mg. of norethynodrel, supplemented by varying amounts of estrogen, on a prescribed day 5 through day 24 regime, resulted in a normal distribution of lengths of menstrual cycles.

B. If this regime is altered by omission of medication, there may ensue either shortened menstrual cycles, caused presumably by withdrawal bleeding, or lengthened menstrual cycles, resulting from adequate maintenance of the endometrium despite intermittent lack of medication or from prolonging of the treatment by use after the twenty-fourth day of the tablets missed earlier.

2. Ovulation.—

A. Presumption of suppression of ovulation is strengthened by the fact that conception did not occur in any instance in which the medication schedule of day 5 through day 24 was followed faithfully.

B. Among those who omitted medication for 3 or more days, the low incidence of pregnancy was roughly proportional to the number of unused tablets.

3. Endometrium.—

A. This compound appeared to exert a prompt progestational effect on the endometrium which, after 5 to 7 days of medication, did not progress in terms of glandular response, but did advance with reference to the stromal reaction.

B. No pathological endometrial changes were observed in specimens taken at different times in the cycle and after varying periods of medication up to 10 months. The sequence of endometrial response to medication, as well as of regression following medication, was generally quite regular, and no distinction could be made between endometrium from short-term and that from long-term treated subjects.

4. Steroid Excretion.—

Studies of urinary excretion of steroids indicated a decrease in 17-hydroxycorticosteroids and, to a questionable extent, of 17-ketosteroids. This decline did not seem to vary with the number of medication cycles, nor did it appear to be accompanied by any discernible signs of adrenocortical hypofunction.

5. Blood Studies.—

No significant differences in hemoglobin level were noted during or after medication as compared with those of untreated women. The average bleeding time, however, both during and after medication, was found to be significantly shorter than in the controls, while the clotting time in the postmedication subjects was significantly less than in either the control or the medicated group.

6. Side Effects.—

A. The treated subjects reported certain untoward reactions, the incidence of which did not vary with 0.8 to 1.8 per cent estrogen supplementation of the 10 mg. dose of norethynodrel.

B. It had been calculated that, over an 18 cycle span of medication, troublesome symptoms would cause approximately 27 per cent of the subjects enrolled in the project to discontinue treatment. Actually, in the course of the study to date, only 18 per cent have ceased medication because of side effects.

C. The administration of a magnesium aluminum glycinate antacid has led to the reported disappearance of untoward reactions in 82 per cent of the subjects who took the antacid.

7. Fertility Control.—

In practice, several difficulties have been encountered in maintaining complete fertility control, so that there have occurred 19 pregnancies, 5 of which were in women who had omitted 3 to 17 tablets from the advised regimen, and 14 in individuals who had stopped medication because of "reactions" or carelessness. These 19 produced a pregnancy rate of 13 per 100 marriage years, which may be compared with an expected incidence of 67 pregnancies per 100 marriage years from Puerto Rican women of this age range not known to be practicing contraception; or an actual incidence of 63 per 100 marriage years among these women (some of whom had been using contraceptives) before entering on the study.

We believe that our data demonstrate the action of a powerful agent for fertility control among the women utilizing it. Thus far, in the subjects of our study, it has clearly lowered the pregnancy rate. The fact that 14 women who had discontinued medication after 1 to 17 cycles became pregnant within 1 to 3 months thereafter suggests that the drug, as thus used, does not interfere with subsequent fertility.

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ADENOMATOID TUMORS OF THE GENITAL TRACT

With Special Reference to the Female

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THE purpose of this report is to present a series of adenomatoid tumors involving the female and also the male genital tracts. Although lesions of this type have been suspected of malignant potentialities,[10, 17] their behavior does not justify such suspicions. Golden and Ash[20] proposed the term "adenomatoid tumor" as being "morphologically correct and genetically neutral," and this nomenclature has been the most commonly used in recent years.

Materials and Methods

Twelve adenomatoid tumors were found in the surgical files of the Institute of Pathology, Western Reserve University, out of some 130,000 specimens examined during a 17 year period (1939-1956). The tissue was fixed in 10 per cent formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin, Heidenhain's iron hematoxylin, elastic van Gieson, Mayer's mucicarmine, and periodic acid-Schiff (PAS) stains. Fat stains (sudan IV) were available on 3 specimens.

Observations

The clinical, surgical, gross pathological, and follow-up information is presented in Table I.

In these 12 cases, the adenomatoid tumors were often incidental. Only 2 of 8 lesions in females were palpated before operation (Cases 3 and 7), while the other 6 were found incidentally in the surgically removed uterus or adnexa. Two of 4 tumors in males were observed as firm scrotal masses and 2 were incidental findings at operation for hydrocele.

No evidence of recurrence or metastasis was found, although follow-up information was not available or adequate in 6 cases.

Pathology

On gross inspection, these lesions were usually firm, discrete, pale gray or yellowish-gray tumors ranging from 0.5 to 7.5 cm. in diameter. Many resembled fibromas or fibromyomas, but some had smoother cut surfaces than most fibromyomas. Three of 5 uterine adenomatoid tumors were accompanied by uterine fibromyomas, as were the one tubal and the one parovarian lesion.

Some of the lesions were encapsulated and others only circumscribed. In Case 10 there was apparent infiltration of the epididymis and rete testis by the tumor.

Microscopically, the adenomatoid tumors had the same characteristic features in both male and female, although there was some variation in the

TABLE I. CLINICAL, SURGICAL, GROSS PATHOLOGICAL, AND FOLLOW-UP DATA IN 12 CASES OF ADENOMATOID TUMORS

CASE	SEX	AGE	RACE	CLINICAL DATA	OPERATION	GROSS PATHOLOGICAL DATA	FOLLOW-UP DATA
1	Female	55	Negro	Descensus of uterus	Hysterectomy and bilateral salpingo-oophorectomy	Firm yellowish-gray nodules on surface of uterus; fibromyomas of uterus	No evidence of recurrence 3 years later
2	Female	63	White	Descensus of uterus	Vaginal hysterectomy	Solitary firm pale gray nodule, 1.0 cm. in diameter, on left lateral wall of uterus	No information
3	Female	27	White	Sterility; mass at fundus on physical examination	"Myomectomy," 3 presumed fibromyomas	Firm, light gray mass, 3.3 cm. in diameter, from right uterine cornu with a slightly bulging, whorled cut surface; also 2 small fibromyomas	No recurrence in 12 years
4	Female	39	White	Relaxed vaginal outlet	Hysterectomy, plastic repair	Single poorly circumscribed firm nodule, 0.6 cm. in diameter, in myometrium with slightly bulging, whorled cut surface	No information
5	Female	53	White	No information	Hysterectomy	Moderately soft 3.5 by 2.0 by 1.5 cm. pedunculated mass beneath serosa near right uterine cornu; small uterine fibromyomas	No information
6	Female	37	White	Menorrhagia	Hysterectomy and right salpingo-oophorectomy	Firm, round, encapsulated mass, 1.0 cm. in diameter, in wall of tube with glistening white cut surface; uterine fibromyomas	No evidence of recurrence 3 years later
7	Female	43	White	Menorrhagia, irregular menses, right adnexal mass	Hysterectomy and bilateral salpingo-oophorectomy	Firm encapsulated mass 7.5 cm. in diameter in posterior leaf of broad ligament attached to right tube and ovary, with smooth yellow-to-pink cut surface; no uterine fibromyomas	No information
8	Female	46	Negro	Abdominal pain, relaxed vaginal outlet, enlarged uterus	Hysterectomy and bilateral salpingo-oophorectomy, plastic repair	Firm nodule 0.5 cm. in diameter in paroovarian connective tissue at one pole of left ovary with white, slightly bulging cut surfaces; uterine fibromyomas	No evidence of recurrence 3 years later
9	Male	51	White	Firm nontender mass noted for 2 months at upper pole left testis	Excision	Firm pale gray 1.4 by 1.0 by 0.3 cm. nodule with smooth cut surface	No recurrence in 8 years
10	Male	?	?	Mass at upper pole of epididymis	Excision	Firm fragments with pale gray cut surfaces mottled with yellowish gray	Living 2½ years later, no other information
11	Male	4	White	Swelling in scrotum for 5 weeks	Right inguinal hernia and hydrocele repaired	Firm pale gray 1.0 by 0.6 by 0.3 cm. nodule loosely attached to wall of hydrocele sac	No information
12	Male	57	White	Left hydrocele for 2 years	Hydrocele repaired; "indurated area" excised from tunica albuginea	Firm gray 1.0 by 0.4 by 0.4 cm. fragment mottled with yellow	No recurrence at autopsy 7 years later (myocardial infarct)

prominence of these individual features from tumor to tumor. They were composed of irregular cell-lined spaces and solid cords of cells in a connective tissue stroma (Fig. 1). Cytoplasmic vacuoles of different sizes were found to some extent in all lesions. These frequently coalesced, suggesting that at least some of the spaces were so formed (Fig. 2). Some spaces were lined by cuboidal or low columnar cells, giving an epithelial or glandular appearance (Fig. 3), while elsewhere flattened cells lined cystic spaces (Fig. 2). The spaces contained a few desquamated cells and occasionally granular or hyaline

Fig. 1.

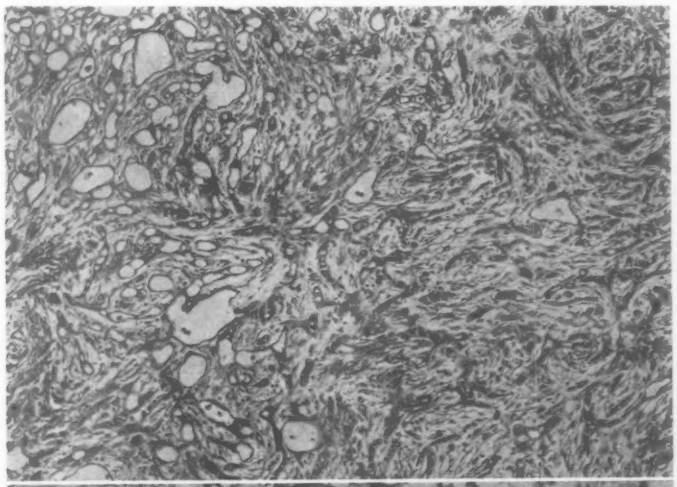

Fig. 2.

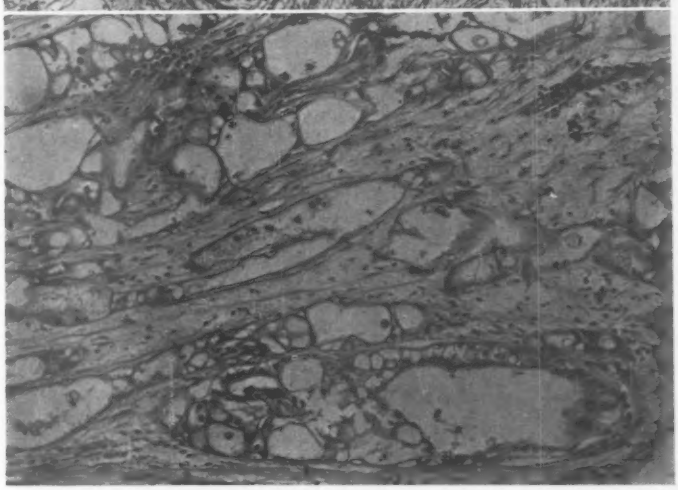

Fig. 1.—Case 6. Adenomatoid tumor of uterine tube showing cystic spaces lined by flattened cells on the left merging into an area on the right with solid cell cords predominating. The latter contain some vacuoles. (Hematoxylin and eosin. ×86; reduced ⅕.)

Fig. 2.—Case 7. Adenomatoid tumor in broad ligament showing cystic spaces and many coalescing vacuoles in lining cells. (Hematoxylin and eosin. ×139; reduced ⅕.)

material which sometimes took the PAS stain but stained weakly at best with mucicarmine. Definite brush borders on lining cells were seen (Fig. 4), with a fine line beneath suggesting a row of basal granules. The brush borders were more apparent in some tumors than others and were best seen on flattened

cells. Definite cilia were not observed. Basement membranes of varying thickness about the cell-lined spaces and cell cords were shown by PAS staining.

The stroma varied somewhat in composition and density. It was mostly collagenous and in some places hyalinized. Smooth muscle was usually scanty and confined to the periphery but in Cases 3 and 4 the glandlike spaces were scattered among muscle bundles which composed the bulk of the tumor. The stroma contained fat in one of 3 specimens stained for lipid (Case 1) but there was no fat in vacuoles or spaces. There was slight infiltration of the stroma of some tumors with lymphocytes, and a few lymphoid nodules without germinal centers were present in some lesions.

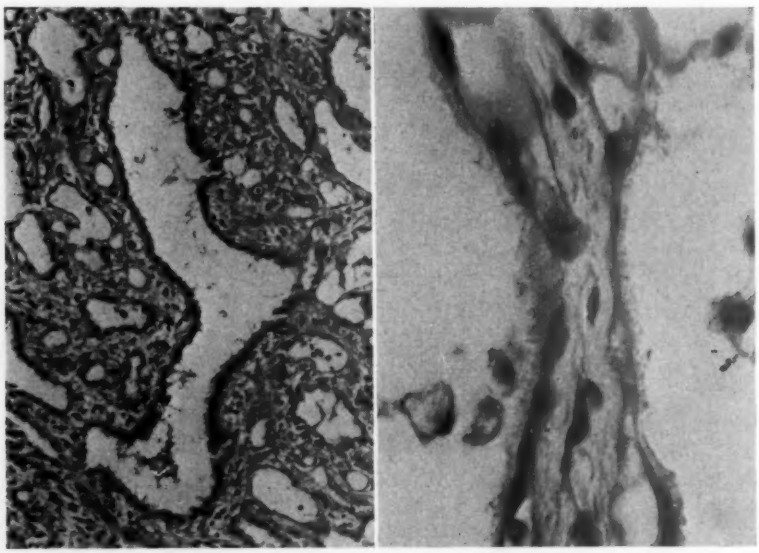

Fig. 3. Fig. 4.

Fig. 3.—Case 5. Adenomatoid tumor of the uterus showing cuboidal and low columnar cells lining some spaces, giving an epithelial appearance. (Hematoxylin and eosin. ×139; reduced ⅕.)

Fig. 4.—Case 7. Adenomatoid tumor in broad ligament showing brush borders on flattened cells. (Mucicarmine stain. ×825; reduced ⅕.)

Review of the Literature and Comment

Many terms have been applied to this tumor. These reflect numerous ideas about its genesis. Besides the term adenomatoid tumor, they include lymphangioma,[24] lymphangioendothelioma,[19] mixed leiomyoma and lymphangioma,[21] angiomatoid tumor or formation,[34] adenoma,[3] adenomyoma,[39] adenofibromyoma,[16] fibromyoma,[41] mesonephroma,[8] mesothelioma,[33] mixed tumor,[44] and low-grade adenocarcinoma.[23]

Location and Morphology.—In the female, Fajers[15] has found 25 acceptable adenomatoid tumors, and later reviews by Lee, Dockerty, Thompson, and Waugh[30] and by Horn and Lewis[25] added some 35 more, including 20 of their own. Evaluation of many of the earlier reports is difficult as some are not illustrated and descriptions are often very brief. With 8 additional recently reported cases[4, 5, 12, 22, 27, 29, 45] and the 8 lesions of this study, the total is at least 76 cases in females.

Of the lesions in females of which the locations are given, 35 were in the uterus, 33 in the uterine tube, 5 in the ovary, one in the broad ligament (Case

7) and one in the parovarian connective tissue (Case 8). In Case 7, the tumor was attached to the tube and the ovary so that its origin is uncertain. Stout[42] mentioned the occurrence of these lesions in the round ligament and canal of Nuck. The approximate location of the more accurately localized tumors is shown in Fig. 5.

Adenomatoid tumors in females are usually described as firm, discrete lesions, but Morehead[34] pointed out that they also occur as scattered "angiomatoid" formations as well as in discrete tumors. They are usually associated with uterine fibromyomas. Most have been subserous.

As adenomatoid tumors in males are of similar appearance to those in females and both involve the genitals, it is generally assumed that they are of similar or homologous origin. Therefore, information about these tumors in males is of interest in the study of lesions in the female, as they are more frequently reported and more often clinically apparent in males.

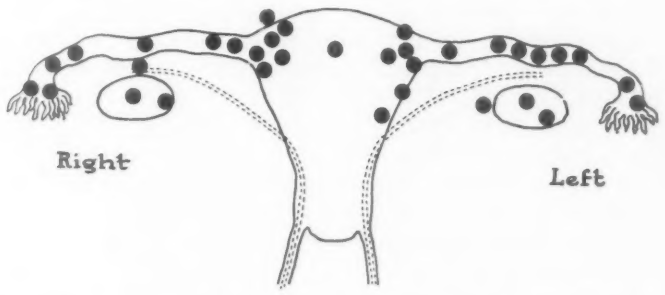

Fig. 5.—Distribution of 34 reported adenomatoid tumors in females, the location of which was given accurately. Location of mesonephric ducts is represented by broken lines. See references 4, 5, 12, 15, 22, 25, 29, and 30, and Cases 2, 3, 5, 7, and 8 of this study.

One hundred and eight adenomatoid tumors in males have been found by Rankin,[38] including 2 cases of his own. Although previous compilations by Fajers[15] and by Lee and associates[30] include a few cases not mentioned by Rankin, evaluation of some of these is difficult, as previously mentioned. Seventeen additional tumors[1, 9, 11, 26, 28, 35, 36, 40, 45-47] in recent years and 4 cases in the present study bring the total to at least 129 cases in males.

Adenomatoid tumors in males are usually reported as small, firm, discrete nodules. They most commonly involve the epididymis but also occur in the testicular tunics and spermatic cord. They constitute the commonest benign tumor of the epididymis.[31] Most are painless and some are present for many years without apparent growth. They have occurred in patients from 5 months[6] to 78 years[23] of age and were bilateral in one case.[35]

There is some difference of opinion about certain histological details but the appearance of adenomatoid tumors is characteristic enough that most writers feel they are discussing the same lesions. Irregular spaces lined by flattened, cuboidal, or low columnar cells are usually described, and vacuoles are almost always noted. Controversial findings such as brush borders,[7, 20, 33] occasional fat in the stroma,[17, 30, 37] and basement membranes[7, 30, 38] are confirmed by the present study, while no definite mucicarmine-positive material,[30, 33] cilia,[30] or flagella[33] were noted.

Histogenesis.—As for origin, many earlier writers considered these lesions lymphangiomas. Morehead[34] favored a vascular origin and compared them to developing vascular spaces. The presence of brush borders is not consistent with this theory, however.

The idea that these lesions are mesotheliomas was first proposed by Masson, Riopelle, and Simard.[33] This theory is partly based on the demonstration of brush borders, flagella, vacuoles, and glandlike formations containing mucicarmine-positive material, all of which are said to be potentialities of mesothelium. Evans[13, 14] and others[1, 30, 32] have demonstrated continuity of the cells lining the spaces of these tumors with the overlying serosa. However, similar continuity has also been demonstrated or claimed between these cells and the epithelium of epididymis,[2] uterine tube,[29] and paramesonephric (Müllerian) duct remnants.[43]

Against both vascular and mesothelial origin is the localization of these tumors in the genitals and immediate vicinity. Evans[13, 14] proposed derivation from the specialized mesothelium of the primitive genital ridge of the embryo. This concept would be in keeping with the distribution.

Some authors suggest origin from mesonephric (Wolffian) primordia or remnants.[3, 16, 45] Sundarasivarao[43] claimed that the distribution in females is against such a theory. Most adenomatoid tumors occur in the tubes and the cornua of the uterus, while the mesonephric tubules and ducts are in the broad ligaments. The ducts enter the uterus laterally in its middle third to descend to the cervix and vagina as Gartner's ducts. No reports of adenomatoid tumors in the cervix or vagina have been found, where they might be expected if they arose from mesonephric remnants. Teilum,[45] however, has cited evidence[18] that the mesonephric and paramesonephric ducts develop in intimate contact and feels that this could explain the distribution on a mesonephric basis.

Efskind[12] and Sundarasivarao[43] suggested origin from primordia or remnants of the paramesonephric duct. The latter author demonstrated continuity of an adenomatoid tumor with such remnants in one case in a male. Continuity of such a tumor with female genital epithelium (of the tube) has been shown only once,[29] however. The paramesonephric ducts arise by infolding of primitive celomic mesothelium, and so the last proposal is not far removed from Evans' suggestion of origin from mesothelium of the primitive genital ridge.

A tentative but reasonable interpretation in view of the location and epithelial appearance of these tumors is that they arise from primitive urogenital ridge structures, such as mesonephric primordia or remnants. Some feel that these lesions may be hamartomas or malformations arising from the primitive structures previously mentioned rather than true neoplasms.[31]

Adenomatoid tumors are benign in their course. Their irregular epithelial appearance has aroused concern about prognosis at times[23, 28] but, as reports of these relatively rare lesions have accumulated, it has become apparent that they do not recur or metastasize. A number of cases have been reported in males and females without encapsulation or even with apparent local infiltration,[10, 23, 34] but no subsequent reports of recurrence or metastasis have been found.

Areas microscopically resembling adenomatoid tumors were noted by Teilum in several tumors involving ovary, uterus, cervix, parametrium, and testis, which he felt were derived from primitive mesonephric mesoderm. Some of these tumors were frankly malignant. Although they may have been related in origin, these neoplasms had features which distinguished them from adenomatoid tumors, such as location and the presence of prominent papillary and tubular formations in many fields.

The problem of treatment arises in males in whom these lesions are often palpable, but in females they are usually recognized only when the surgical specimen is examined microscopically. Rarely, they have been identified in females at operation and removed locally from the uterus.[30] It is suspected

that many of these lesions are overlooked in myomatous uteri, without apparent clinical consequences. In the absence of reported malignant behavior of adenomatoid tumors, it is reasonable to treat them by local excision.

Summary

A group of 12 adenomatoid tumors, uncommon lesions involving the female and male genital tracts, is presented. Their origin is still a controversial matter, but it seems likely that they arise from primitive urogenital ridge structures either as hamartomas or true neoplasms. As no cases with definite malignant behavior have been reported, local excision seems indicated for these benign lesions.

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CONDYLOMATA ACUMINATA OF THE CERVIX

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POLYPOID lesions of the cervix, other than the common "cervical polyp," have received little attention until the past few years. In spite of increased interest in such lesions, there is still confusion as to terminology and as yet only a relatively small number have been reported. In 1921 Wharton[10] reported 3 cases and commented on the rarity of the lesion. Robert Meyer[7] in 1922 made one of his usual outstanding contributions, although he was primarily interested in the malignant potentialities of these tumors. In his small group of 6 collected cases he differentiated five variations of this type of lesion. He did not actually describe a condyloma of the cervix but rather compared the papillary lesions in his series with the general description of the condyloma. Two cases were associated with pregnancy and there was one papillary squamous carcinoma. Meyer noted that mistakes were made in pathological interpretation in 2 cases, a feature mentioned again recently by Greene and Peckham.[3] Cullen also stated that condylomas of the cervix in pregnancy may be mistaken for carcinoma.

Only isolated cases were reported from 1922 to 1945 when Edmondson[1] and associates collected 6 cases, 5 of which were found in pregnant women and the sixth in a patient possibly pregnant at the time. They divided the lesions into three groups depending on configuration of the epithelium, namely: (1) hyperplasia with large rete cones and narrow connective tissue papillae, (2) nodular pearly lesions with thicker epithelium, and (3) gross papillary lesions or condylomata. Vacuolization of the cells was noted in the "older" lesions but no mention was made of hyper- or parakeratosis as a means of differentiation. The authors noted that "condyloma" in the nonpregnant cervix was very rare, only one instance having been found in the records of the Los Angeles County Hospital.

Hill[4] in 1948 recorded one case in pregnancy in which pathologists differed as to the presence of malignancy. In the follow-up after cesarean section, however, the cervix appeared normal. Wolfe[11] also recorded one case in pregnancy with postpartum regression without therapy. He noted in the microscopic pathological examination the presence of parakeratosis and vacuolization of the cells with markedly thickened rete pegs and nuclear variations with mitosis.

In 1952 Marsh[6] reviewed the literature, collecting 23 cases, 15 of which were associated with pregnancy. He added 8 of his own cases, in 4 of which the patients were pregnant. The diagnosis of condyloma was made only if other condylomatous lesions were present elsewhere. The microscopic picture

described by Marsh as typical of the "papilloma" of the cervix is "a papillary structure composed of hypertrophic, hyperplastic, stratified squamous epithelium, the cells of which are quite regular. It is supported by a delicate connective tissue framework which is infiltrated moderately with small mononuclear cells. Focal areas of spongiosis and transmigration of leukocytes are noted in the epithelium."

Also in 1952, Goforth,[2] in a report entitled "Squamous Cell Papilloma of the Cervix," divided cervical lesions into (1) papilloma, a localized neoplastic surface epithelial proliferation, and (2) polyp, an irritative reactive or inflammatory localized hyperplasia. The papillomas were subdivided into: (a) squamous-cell papilloma, and (b) rare gland-cell papillary adenoma. The polyps are subdivided into (a) condylomatous polyps of probable viral origin not related to neoplastic disease; (b) simple inflammatory polyps; and (c) polypous hyperplasias of pregnancy, probably hormonal in origin. The author reported 21 cases found in 600 biopsies taken in 4 years. Nineteen lesions were benign and 2 malignant. There was only one pregnant patient in the series. The ages ranged from 8 to 42 years.

In 1954, Raffery and Payne[8] reported on 19 condylomata of the cervix found in 587 cervical biopsies over a period of 5 years and concluded that this lesion is by no means rare. About 50 per cent of the patients were pregnant. The ages ranged from 8 to 32 years. In 5 of the 19 cases, a gross diagnosis of carcinoma was made. A specific definition of the lesion is given as a "cauliflower" growth with:

A. Thick papillary stratified squamous epithelium
    1. Acanthosis
    2. Parakeratosis
    3. Cytoplasmic vacuolization
    4. Intranuclear inclusions

B. Fine dermal fronds
    1. Quantitatively scanty
    2. Frequently edematous
    3. Diffusely and focally infiltrated by chronic inflammatory cells

Greene and Peckham[3] reported 26 cases of squamous papilloma of the cervix. Fifteen of the patients were pregnant and in most of these the lesions regressed spontaneously post partum. None of the patients had lesions of the vulva, and only one of the vagina; however, one patient had diffuse involvement of the endometrium. Another had a microscopically benign lesion which, however, was locally invasive and fatal. The same course of events has recently been recorded in similar lesions of the vulva. The microscopic picture described by the authors showed no vacuolization of the cells, some hyperkeratosis, but only one example of parakeratosis.

Kistner and Hertig[5] reported on 14 instances of "papillomas of the uterine cervix" and divided the cases into three groups, namely: (1) 5 cervical papillomas associated with pregnancy, (2) 2 condylomata acuminata, (3) 7 true papillomas. The difficulties of diagnosis, both gross and microscopic, are stressed, especially in the groups which the authors consider to be "potentially or actually malignant."

In summary, then, 111 cases of various papillary lesions of the cervix have been reported under various captions. Forty-five of the patients were pregnant at the time of the study and apparently most of these lesions regressed spontaneously post partum. Six patients developed or had malignancy associated with the papillary lesion and in several others the diagnosis of carcinoma was made erroneously. On the other hand, one lesion was treated as benign and proved fatal in about a year. These mistakes, from both points of

view, demonstrate the confusing pictures that these lesions may present to the pathologist. Similarly the gross lesions may appear as condylomas, papillomas, granulomas, polyps, leukoplakia, or carcinomas.

In addition to the confusion as to the activity of the lesions, there is obviously a great difference of opinion concerning a satisfactory terminology and the microscopic picture which corresponds to these lesions. As previously noted, Meyer attempted to divide these lesions into two main groups, namely, the condyloma-like lesions of probably inflammatory origin and the true new growth. Studying lesions of this type in the files of the gynecological pathology department of the Johns Hopkins Hospital, we have also come to believe that these lesions fall into two main groups. We, however, feel that they can be separated on a histological basis in a majority of instances.

Criteria for Diagnosis

In order to avoid perpetuating the existent present confusion as to what exactly constitutes a condyloma acuminatum it is expedient to establish our criteria for this diagnosis. It is our belief that the cervical condyloma acuminatum presents a definite histological picture (Figs. 1 and 2) characterized by: (1) elongation and thickening of the rete pegs, (2) marked acanthosis, (3) parakeratosis, (4) papillomatosis, mild, and (5) cytoplasmic vacuolization.

The rete pegs invariably show elongation and thickening, the degree depending probably upon the age of the group. This is perhaps the earliest change produced by this lesion. Branching of the rete pegs (Fig. 1) is often prominent and may present a confusing or suspicious picture to the untrained eye. This is especially true if the tissue is cut tangentially; however, the basement membrane is well defined and cellular activity is generally within normal limits.

Acanthosis (Fig. 1) is one of the most prominent features of the condyloma acuminatum, and often is of a marked degree. Despite this hypertrophy of the prickle-cell layer, the epithelium usually maintains an orderly arrangement and neoplasia can generally be readily dismissed. The acanthotic layer shows a variable amount of cytoplasmic vacuolization which is generally most marked in its upper portions. The presence of these cytoplasmic vacuoles has been stressed by others. It is a feature of so many different cervical lesions, however, that its value as a diagnostic tool may be open to question. When the vacuolated cells are larger and more irregular than their counterparts it appears to be of value as a positive finding. More important, however, is its absence, in which instance one should be doubly certain about the other characteristics of the growth before establishing a positive diagnosis.

Parakeratosis (Fig. 2) is rather consistently noted to a varying degree and is probably most marked in the older lesions. It should be differentiated from hyperkeratosis which we feel is only rarely noted and then to a minimal degree in the condyloma. As a consequence, the granular layer (stratum granulosum) is rarely seen in this lesion.

Although intranuclear inclusion bodies are reported to occur generally in nuclei showing fragmentation, it is questionable whether they are found consistently enough to be of value from a diagnostic point of view. Searching for them requires very high magnification and infinite patience. Their presence may, however, be of value in establishing a diagnosis in an otherwise questionable section.

Papillomatosis (upward proliferation of the papillae) produces the characteristic papillary or treelike pattern. These papillae are invariably narrow and delicate, often edematous, and show a rather consistent chronic inflammatory infiltrate. They may fail to show the degree of acanthosis noted in the

rete pegs when sectioned in the terminal portion of the papillary processes, and consequently the stratified squamous epithelium covering the papillae appears relatively thin.

Fig. 1.

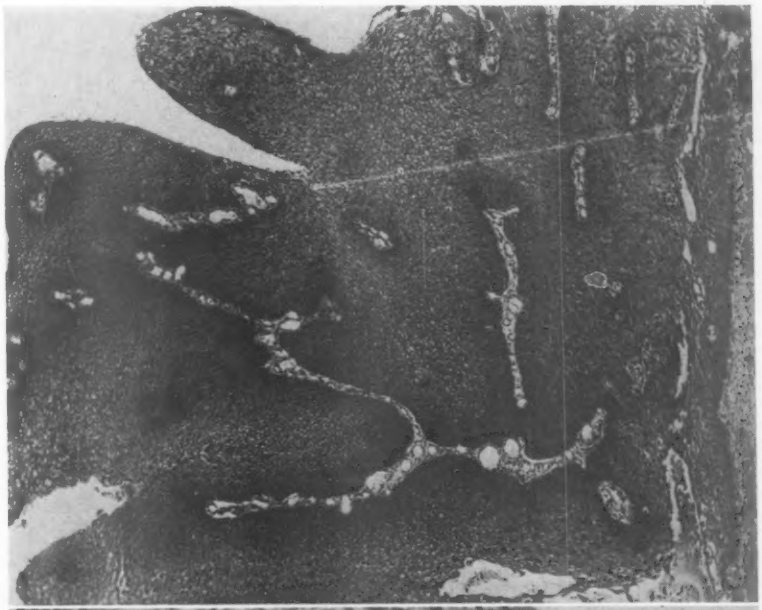

Fig. 2.

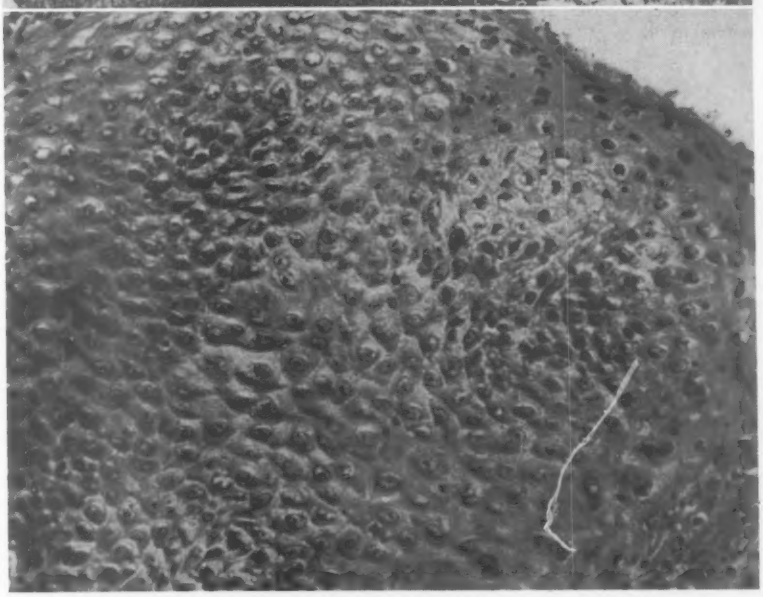

Fig. 1.—Showing characteristic pattern of condyloma with acanthosis, branching of rete pegs, and slight papillomatosis.

Fig. 2.—High power of the condyloma showing parakeratosis. (×300; reduced ⅓.)

The squamous papilloma or "true papilloma" (Fig. 3) can usually be differentiated from the condyloma acuminatum by the presence of hyperkeratosis and often a granular layer (Fig. 4), more prominent papillomatosis,

minimal or absent vacuolization, and a lesser degree of acanthosis. Other features are less diagnostic and will not be included in this study.

Fig. 3.

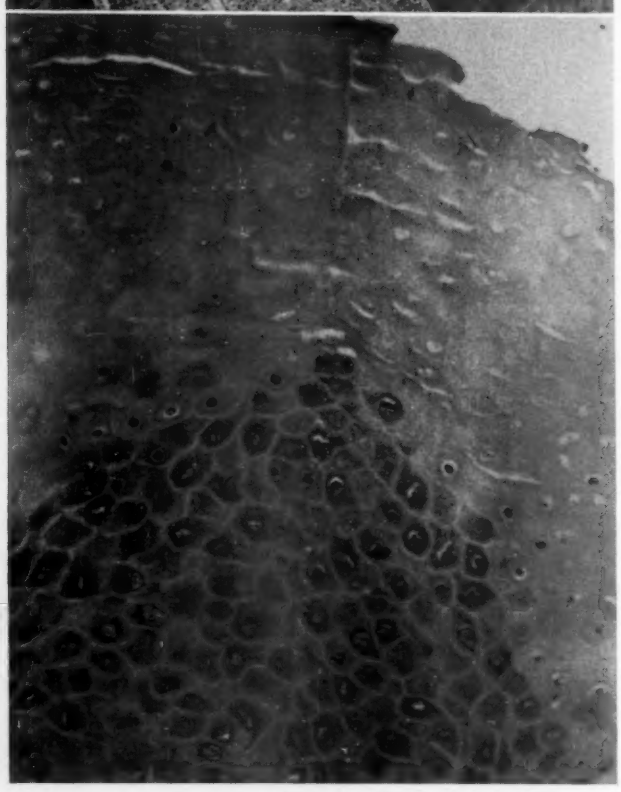

Fig. 4.

Fig. 3.—Papilloma showing wavy surface outline and hyperkeratosis.

Fig. 4.—High power of squamous papilloma showing hyperkeratosis and presence of granular layer. (×300; reduced ⅓.)

These histological requirements for the diagnosis of certain condyloma acuminatum, and its differentiation from the squamous papilloma are not altogether new for they have been reported in part by others. This may be, however, the first report to offer as comprehensive a histological picture of the condyloma acuminatum of the cervix and restrict its diagnosis to this description.

Study Group

Fifty-five cases had been classified as condylomas of the cervix in the files of the gynecological pathology department at the Johns Hopkins Hospital between the years 1945 and 1955. During this time approximately 60,000 specimens had been processed. Of the 55 cases, 16 were eliminated as not satisfying the minimal microscopic criteria to justify the diagnosis of condyloma. In the remaining 39 cases, there were 3 which showed characteristics of both condyloma and papilloma; the former was considered the more prominent, however.

Fig. 5.—Condyloma showing characteristic pattern with some mild degree of papillomatosis.

Clinical Features.—The patients were for the most part in the third and fourth decades of life, varying in age from 15 to 35 years. There was no striking racial variation. Of the 39 patients, 7 were pregnant at the time the lesion was noted. Pregnancy and condylomata were less commonly associated in the present series than in most others reported.

Treatment in general consisted of biopsy and cauterization. Podophyllin was used in one case with success. Conization was performed in the case in which a diagnosis of carcinoma in situ was made. It seemed justifiable, in the 26-year-old patient with a single warty lesion, to employ this type of therapy if thorough follow-up was insisted upon. Finally, one case was treated with radium in the mistaken opinion that carcinoma was present. This patient has remained well to date.

Microscopic Data.—The main microscopic characteristics of these lesions have been studied in each individual case and the outstanding points may now be set down. The more diagnostic features are parakeratosis, acanthosis, and papillomatosis. Parakeratosis and acanthosis are the most prominent microscopic findings when the condyloma appears on the exposed epithelial surface (e.g., the vulva), and in our experience the same seems to be true when the lesion occurs on the cervix. As keratin is not found in the normal cervix a granular layer is never seen. Cervical condyloma may rarely show keratin formation with a coinciding granular layer; it is, however, always patchy and minimal in degree. It is this absence of a granular layer and hyperkeratosis that distinguishes the condyloma (Figs. 1 and 2) from a squamous papilloma (Figs. 3 and 4) in which these features are prominent findings. Parakeratosis (Fig. 2) therefore, is the prominent feature of the superficial layers of the condyloma acuminatum. Minor degrees of papillomatosis were frequently noted and, although not as striking as the acanthosis, were still a feature of the condyloma (Fig. 5).

Fig. 6.—Condylomatous lesion of the vulva which was clinically malignant with invasion of the pubis at the time of initial surgery.

These changes may be seen in the various verrucous lesions described in dermatology texts. Hyperkeratosis is in general, however, a very prominent feature of these conditions, at least in certain areas, and the granular zone is more evident. Furthermore, vacuolization of the cells is generally a striking feature of the true verruca and other lesions in which epithelial proliferation is pronounced, whereas it is present to only a moderate degree in the condyloma. The verruca, in addition, is a very rare lesion of the cervix, as Meyer's case is the only one reported in the literature. The presence or absence of such vacuolization, however, seems to play no important role in the diagnosis or in the malignant potential of these tumors. In one case inclusion bodies were described but no special studies were done on this tissue. These lesions,

like other warty lesions, are nonetheless felt to be viral in origin. Finally, inflammatory infiltrate is frequently seen in the underlying corium, but is rarely extensive.

The degree of hyperactivity of the epithelial cells deserves some discussion. Although these lesions are considered to be benign, nevertheless malignancies of the vulva have been described in which the initial lesion was condylomatous and in which the gross appearance was that of a warty growth.

Fig. 7.

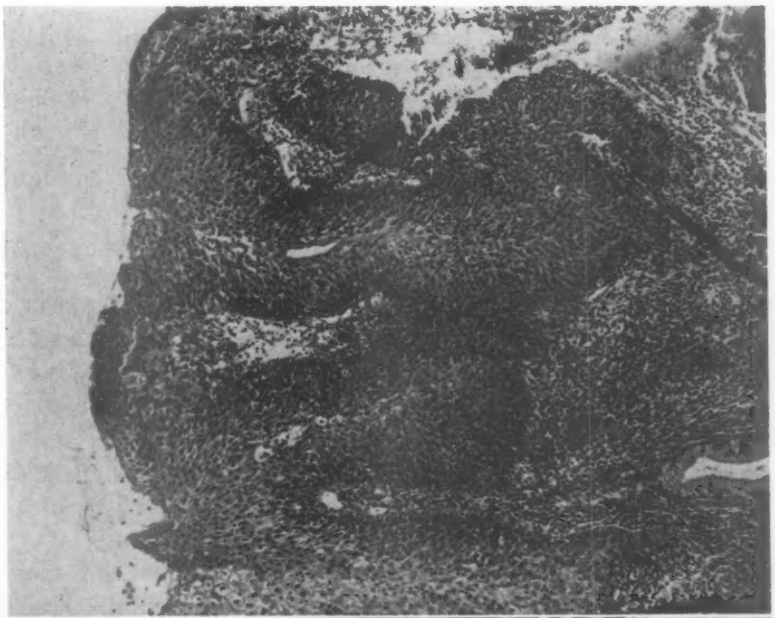

Fig. 8.

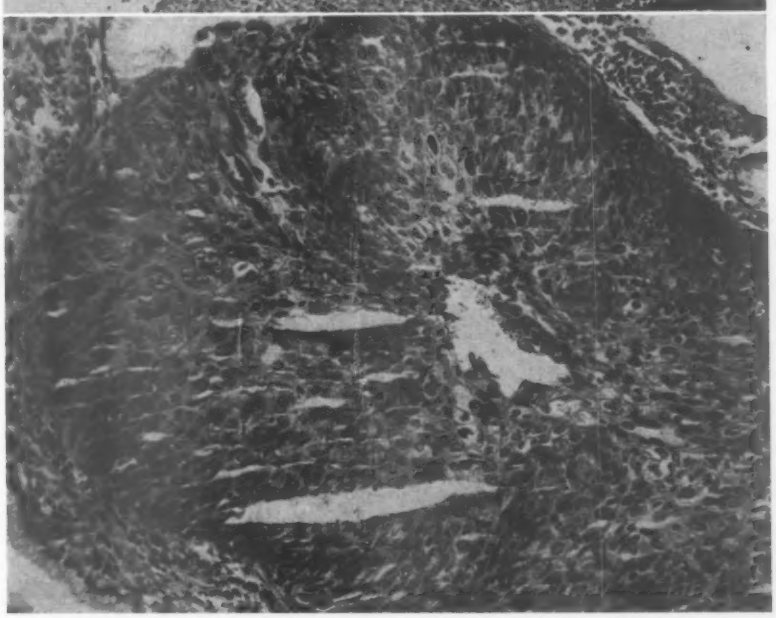

Fig. 7.—Condyloma showing some epithelial hyperactivity in the rete pegs.

Fig. 8.—Condyloma with marked cellular changes involving the underlying gland felt to be carcinoma in situ.

It is also well recognized that great difficulty may be encountered in diagnosing malignancy in these more well-differentiated lesions. Greene and Peckham reported such a case in their study of squamous papillomas, namely, one in which the diagnosis of carcinoma was not made on the initial study and there was a difference of opinion on subsequent biopsies; however, the patient died of carcinoma. A similar situation was present in a case of condyloma of the vulva reported by one of us (J. D. W.) in which a microscopic diagnosis was not established. The patient went on to die of her disease, however, in spite of extensive surgery (Fig. 6). These cases demonstrate the mistakes that can be made in the microscopic interpretation of these conditions.

In the present study 9 cases were felt to demonstrate mild degrees of epithelial hyperactivity (Fig. 7) and in one case the changes were characterized as moderate. In only one instance was the diagnosis of carcinoma in situ made (Fig. 8). Cauterization had been employed in all cases of hyperactivity with the exception of one treated with radium. The lesion diagnosed as carcinoma in situ was treated by conization. No invasive malignancy had developed in any case as far as can be determined.

Comment

In this study of 39 cases of condylomata acuminata of the cervix, certain microscopic criteria are described which validate the diagnosis. Points of differentiation from other warty and papillomatous lesions are noted and stressed. Although there is a degree of overlapping of certain features, nevertheless, the major characteristics were primarily parakeratosis and acanthosis with elongation and thickening of the rete pegs. Minor degrees of papillomatosis and vacuolization of the cells were frequently seen but were of rather secondary importance diagnostically.

Malignant change is as rare in these lesions as it is in vulvar condylomata, but may be somewhat troublesome due to the differentiation of the cells. In this series, hyperactivity was noted in a few cases, and there was one instance of carcinoma in situ. No instance of invasive malignancy was found in the group, however, and none has developed during the follow-up as far as can be determined.

Summary

1. Thirty-nine cases of condylomata acuminata of the cervix were studied.

2. Microscopic criteria for the diagnosis of this lesion and differences between condyloma and squamous papilloma are suggested.

3. Malignant change is a rare finding in condylomata, although confusing pictures are seen.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Abdominal Operations by the Vaginal Route. By Paul Werner and Julius Sederl. 165 pages, 120 plates. Philadelphia, 1958, J. B. Lippincott Company. $9.00.

A clear exposition of the authors' thinking is presented in this monograph on the vaginal approach to abdominal operations. The contents range from the typical procedures such as vaginal hysterectomy to the unusual, like oophorectomy.

The illustrations are large, clear, and topographic.

As is often the case with meticulous surgeons, considerable attention is lavished on the preoperative care and the types of instruments employed.

In the opinion of the authors, severe pelvic adhesions are not viewed as deterrents to vaginal extirpation of the uterus. They advocate splitting the uterus in the midline in such cases. It would be interesting to see their principles applied to patients with severe chronic pelvic inflammatory disease.

In view of the authors' plea for fuller utilization of the vaginal approach, it is of interest to note that the book is dedicated to the master, Wertheim. Elsewhere, the authors have discussed and defended the Wertheim hysterectomy. In such a book as this, one would have welcomed the inclusion of the Schauta vaginal hysterectomy.

Documentation of their results in terms of mortality, morbidity, success and failure rates would have added considerably to our appreciation of the material presented.

Studies on Fertility. By R. G. Harrison. 138 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. $5.00.

The collection of papers published in this edition (Vol. 8 of the *Proceedings of the British Society for the Study of Fertility*) represents the main trends in current research in the field of infertility. To a certain extent, the 13 articles presented in the book reflect more advanced thinking rather than useful clinical teaching. Of the total, the majority of which were given at the 1956 meeting of the Society, the first 3 papers are concerned with fertility in the human male, the following 7 with studies in the male experimental animal. The last 3 articles are devoted to fertility in the female (2 in the human and 1 in the experimental animal).

One of the most stimulating and at the same time one of the most thorough reports is that of Clare Harvey, entitled "The Use of Partitioned Ejaculates in Investigating the Role of Accessory Secretions in Human Semen." The first and second fractions of almost 400 ejaculates were carefully investigated for distribution of spermatozoa, fructose, and citric acid. As a result of extensive biochemical assays and microscopic studies, the author evolved an explanation as to how the various components of human semen are assembled immediately prior to ejaculation.

Another interesting paper consists of a short account by J. H. Carver of the results of 68 testicular biopsies, showing a wide variation in the histologic pictures in cases of azoospermia and oligospermia. In a brief report by I. G. White involving "Studies Relating to the Mammalian Spermatozoa," metabolic experiments were conducted on spermatozoa which thawed after deep freezing with glycerol. The author demonstrated that, after deep freezing, ram and bull spermatozoa behaved disappointingly from the metabolic point of view, even though initial revival seemed to be good. The experiment suggested that the glycerol effect was mainly through its protective action on sperm colloids, probably because of its high electrolyte and water-binding capacity.

In an article entitled "The Influence of Seminal Fluid on Fertility," by N. T. Werthiessen, W. Marden, F. Haag, and J. W. Goldzieher, a bioassay technique for measurement of sperm motility-maintaining capacity of seminal fluid is described. According to their method, seminal fluids were shown to vary greatly in their motility-maintenance capacity. The authors found that the nonprotein sulfhydryl concentration varied inversely as the motility-maintenance capacity and correlated well with the actual fertility as studied in over 1,300 copulations in horses. A comparable relationship between motility-maintenance capacity and sulfhydryl concentration was also demonstrated in the human.

Heart Disease in Pregnancy. Physiology and Management. By C. Sidney Burwell and James Metcalfe. 349 pages, 44 figures and tables. Boston, 1958, Little, Brown & Company. $10.00.

This book reads like a breeze, both because it is well written and because the physiology is rather shallow. Essentially, the book is an expanded paper reporting the authors' experience with 355 pregnancies in women with heart disease. Rheumatic heart disease made up 84 per cent of the cases and congenital heart disease 14 per cent. In order to cover the other important varieties of heart disease, the authors give brief summaries of selected papers from the literature.

Many of the data available in published reports are not used in discussing cardiovascular physiology. For instance, the cardiac output in pregnancy is said to reach a maximum in the eighth (calendar) month and most of the argument is based upon measurements that Burwell made with the acetylene method 20 years ago. The chief virtue of this old study is that the 4 normal women were followed with repeated measurements throughout most of pregnancy (2 more cases have been added since). Curiously, the peak outputs in these women occurred in the twenty-third, twenty-fourth, thirtieth, and thirty-first weeks, but the curve shown depicts the maximal output as occurring later than any one actually did. Figure 8 shows a good parallelism between these data and the data from a "modern" study by Hamilton, who used cardiac catheterization and the Fick principle. In her study, however, the position of the catheter was not controlled (*assumed* to be in the auricle and even if it were, mixed venous blood may not have been obtained). Also, arterial saturation was not measured, but assumed to be 95 per cent, and the oxygen consumption was not measured at the time blood samples were taken. There are several better studies, but they would not show so good a correlation with the acetylene measurements, or with the incidence of cardiac failure by months of gestation (Figure 25). Similarly, the plasma and blood volumes are repeatedly said to follow a curve parallel to that shown for cardiac output, and the barest mention is made of the fact that one of several workers has failed to find decreases in the last weeks of pregnancy.

In Hamilton's experience at the Boston Lying-in Hospital, about 6 per cent of the patients with diagnoses of rheumatic heart disease had mitral insufficiency as the predominant valvular lesion. In the present series, from the same clinic, 24 per cent of the cases are so diagnosed despite the authors' cautioning the reader against overdiagnosis of heart disease in pregnant women, where a whole constellation of signs and symptoms may mimic mitral insufficiency.

In the 298 pregnancies associated with rheumatic heart disease there were 3 maternal deaths, at least one of which followed therapeutic abortion. The perinatal mortality was 18 per cent, half of which was contributed by therapeutic abortions. But for the latter, the perinatal loss would be close to that of the whole clinic population. In the first year of the authors' experience at the Boston Lying-in Hospital, therapeutic abortion was done in 18 per cent of the patients. This incidence has decreased and they write (in italics) "It is our current position (*from which we are prepared to retreat occasionally*) that *any cardiac patient is entitled to a trial of pregnancy.*" The principles of management developed by Hamilton (and by Gorenberg) do succeed in "*more than 97 per cent of all cardiac patients who are capable of achieving pregnancy*" (authors' italics).

The book is well printed, the illustrations are good, italics are perhaps overused, cesarean is misspelled more often than not, and the text is a "which-hunter's" paradise.

Eden and Holland's Manual of Obstetrics. By Alan Brews. 751 pages, 371 illustrations. Boston, 1957, Little, Brown & Company. $11.00.

This stout and handy volume has now gone through eleven editions since 1906, which is a clear indication that it possesses considerable merit. Now thoroughly revised and with many new illustrations added, it gives up-to-date information in a concise and readable form.

The methods set forth are conservative and in keeping with sound obstetric practice. Apparently there is very little divergence in viewpoint between authorities in Great Britain and in this country.

The Barton forceps are mentioned only in connection with the use of the posterior blade for delivery of the head in cesarean section. Although the Kielland forceps are described, there is no mention of forceps rotation in face presentation with the chin posterior. Digital "stretching" of the cervix is advocated.

Guides to further reading, including a number of American contributions, and a good index are provided. The illustrations, including a number of fine color plates, are excellent.

SELECTED ABSTRACTS

Acta Cytologica (a New Journal)

Vol. 1, 1958.

*Symposium on Dyskaryosis, p. 1.

Symposium on Dyskaryosis, p. 1.

This is the first issue of a new journal which will be the official periodical of the International Academy of Gynecological Cytology. It contains the recordings of three symposia but only one, "Symposium on Dyskaryosis," will be abstracted.

The above-mentioned symposium occupies 39 pages of fine print covering numerous aspects of dyskaryosis. It is impossible to cover all aspects but some of the important features will be mentioned. Thirty-three world authorities on cytology entered into the discussions with some differences of opinion which makes for interesting reading.

The definition of dyskaryosis is discussed thoroughly and it is agreed that a dyskaryotic cell is a squamous cell containing a typical malignant nucleus, but differs from a true cancer cell in having adequate cytoplasm and a cytoplasm-nuclear ratio within normal limits. The cytochemistry of dyskaryostic cells is quite adequately covered.

The relationship of Trichomonas infestation to abnormal cellular development is discussed in great detail and there is some difference of opinion. Some members believe that Trichomonas infestation does not cause cellular changes that should be confused with malignant changes whereas others do.

The most spirited discussion involves the relationship of the "pre-cancer complex" to dyskaryosis. It appears that most workers believe that the two are the same. The discussion makes interesting reading.

The abstractor found this new journal most informative and believes it will be an important reference. It is hoped that the future issues will maintain the same high standard.

J. Edward Hall

Acta Obstetrica et Gynecologica Scandinavica

Vol. 36, Supplement 3, 1957.

*Malmstrom, Tage: The Vacuum Extractor: an Obstetrical Instrument, and the Parturiometer: A Tokographic Device, Supp. 3.

Malmstrom: The Vacuum Extractor: an Obstetrical Instrument, and the Parturiometer: A Tokographic Device, supp. 3.

The author has made an extensive investigation of the basic mechanical principles for the design and use of an obstetric instrument which he has called the Vacuum Extractor (VE). The instrument was designed as a suction cup and it has been developed into a traction device which can be attached firmly to the preceding part of the fetal head without significant traumatization to the scalp. The various sizes of the instrument's cups allow the obstetrician to introduce and attach the Vacuum Extractor at a high, mid-high, or low station of the fetal head without having to wait for perfect dilatation of the cervix. By employing an intermittent traction technique, synchronized with the uterine contractions, the author was able to reinforce labor; and by varying the direction of traction, it was possible to correct abnormal presentation or position of the fetal head.

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*Titles preceded by an asterisk are abstracted below.

The author has also elaborated an apparatus called the Parturiometer (PM), a tokographic device with two kinds of receptors, one for external and one for internal measurements of intrauterine pressures. The principle of the external technique is to convert the abdominal wall into a pressure-transferring membrane, while the internal recording technique combines the receptor with a small suction cup brought into close contact with the amniotic membrane by creating a vacuum. A close similarity was noted in the recording of intrauterine pressures by the two techniques.

An analysis of the recordings led to the conclusion that the amniotic pressure is uniformly distributed throughout the amniotic fluid and the fetal body; thus, the fetal body functions as a "liquid body" in relation to the intrauterine pressure. The investigation of the pressure distribution in the fetal body led the author to think of the propulsive force during labor as an extractive force acting on the preceding part of the fetal head. According to him, this information allows him to use the Vacuum Extractor in a more scientific manner by adding an extractive force, in cases of abnormal labor, in a physiologic manner.

ROBERT E. L. NESBITT, JR.

Vol. 36, Supplement 4, 1957.

*Lundgren, Nils: Studies on the Vasculature of the Corpus of the Human Uterus, Supp. 4.

Lundgren: Studies on the Vasculature of the Corpus of the Human Uterus, supp. 4.

The author has made an extensive investigation of the topography of the vessels within the human uterus in different cyclic phases, the relationship between these vessels and the myometrium, and has correlated the morphologic changes with function. The blood vessels of 172 uteri removed at operation were studied on the basis of injected specimens, serial sections, and reconstructions.

From their origin in the arcuate arteries the centripetal arteries run radially toward the endometrium. They are end arteries and divide repeatedly on their way. In the myometrium the absence of anastomoses is compensated by the large number of centripetal arteries per unit of area with lateral branches from adjacent arteries extending into one another's field of supply. Also, in the inner two thirds of the myometrium the veins run parallel to the muscle bundles and, like the latter, cross one another at varying angles to form a plexus.

The basal part of the endometrium receives its supply not only from the coiled arteries, but also from the centripetal arteries in the inner layer of the myometrium. This is not the case in the superficial part of the endometrium, which is thus supplied by a terminal circulation. In their course in the endometrium, the coiled arteries give off branches to the stroma and the glands; some of them split up into tufts in the basal parts of the endometrium. The number of lumina in an arterial field depends on whether the field is made up of loops from one artery or from several as well as on the direction of the section in relation to the general course of the artery. Thus, the increased size of the fields during the secretory phase cannot be accepted as evidence of increased tortuosity of the arteries. The coils in the arteries are continuously changing and may be due to contractions of the myometrial muscle bundles entering their walls. The contractions of the myometrium are transmitted to the endometrium by way of anisotropic fibrils and thereby probably facilitate the emptying of the glands and the drainage of the veins by varying the shape of the lumina.

The role that has hitherto been attached to the tortuosity of the coiled arteries as a cause of bleeding appears now to be debatable, but the author emphasizes that the correlation of these anatomic observations with function is difficult. It is probable, however, that venous stasis results in degenerative changes in the arterial walls, which respond with partial contractions contributing to and accelerating necrosis of the superficial part of the endometrium. The basalis with its more abundant blood supply does not show such advanced necrotic changes.

ROBERT E. L. NESBITT, JR.

Journal of the American Geriatrics Society

Vol. 6, No. 2, February, 1958.

*Pisani, Bernard J.: Term Gestation Following Total Gastrectomy, p. 99.

Pisani: Term Gestation Following Total Gastrectomy, p. 99.

Herein is reported the first instance of pregnancy occurring in a woman of 41 who had had a total gastrectomy 4½ years before the pregnancy, in 26,979 deliveries at St. Vincent's Hospital in New York City.

The patient developed an acute spontaneous hemorrhagic gastritis which required an esophagoduodenostomy. Subsequently, she received weekly injections of vitamin B_{12} and biweekly injections of iron. Though previously involuntarily sterile, she became pregnant at the age of 41. She was found to have fibromyomas of the uterus as well.

During the pregnancy, which was quite uneventful, she received 25 to 50 mcg. of vitamin B_{12}, 1 ml. of liver concentrate, and 2 ml. of iron-dextran complex at weekly intervals. She was delivered normally of a 2,700 gram female child and the puerperium was normal.

DAVID M. KYDD

The Journal of the American Medical Association

Vol. 166, January 11, 1958.

*Finnerty, F. A., Buchholz, J. H., and Tuckman, John: Evaluation of Chlorothiazide (Diuril) in the Toxemias of Pregnancy, p. 141.

*Burwell, C. S.: The Special Problem of Rheumatic Heart Disease in Pregnant Women, p. 153.

Finnerty, Buchholz, and Tuckman: Evaluation of Chlorothiazide (Diuril) in the Toxemias of Pregnancy, p. 141.

It was found that chlorothiazide is a potent diuretic and hypertensive agent in the treatment of the toxemias of pregnancy. One hundred and forty-four patients were evaluated. The average effective dose was 1 Gm. per day by mouth. The drug enhances sodium and chloride excretion by a direct effect on renal tubular transport mechanisms. Chlorothiazide and acetazoleamide (Diamox) used in combination obtain a better diuretic effect and reduction of blood pressure than when used individually. It was felt by the authors that the usual excellent response, combined with the absence of significant toxicity and the lack of development of drug resistance, makes chlorothiazide ideal for the prevention and treatment of toxemia.

ROBERT C. KNAPP

Burwell: The Special Problem of Rheumatic Heart Disease in Pregnant Women, p. 153.

The author discusses his vast experience with heart disease in pregnancy. Of 277 pregnant women with cardiac disease, 85 per cent had rheumatic heart disease; the predominant lesion was mitral stenosis. He notes the adverse effect of the physiological changes which occur during pregnancy on this condition. The increased cardiac output contributes to pulmonary hypertension, the accelerated heart rate may precipitate pulmonary congestion, and an increase in total blood volume can lead to an increase in the pressure level in the left atrium. With understanding and application of the principle of the total cardiac burden in relation to the patient, good management of the pregnant patient with heart disease can be carried out. Termination of the pregnancy is rarely necessary and cardiac surgery should be postponed until pregnancy has been completed. Good conservative medical management is the most successful.

ROBERT C. KNAPP

Journal of Obstetrics and Gynaecology of the British Empire

Vol. 64, December, 1957.

*Seftel, H. C., and Schewitz, L. J.: The Nephrotic Syndrome in Pregnancy, p. 862.

*McFarlane, C. N., and Truelove, L. H.: Addison's Disease in Pregnancy, p. 891.

Seftel and Schewitz: The Nephrotic Syndrome in Pregnancy, p. 862.

The authors make a plea for the conservative attitude toward and a more hopeful prognosis for patients with the nephrotic syndrome in pregnancy. Under careful supervision they favor allowing patients with this disease to proceed to term.

The report consists of 7 cases, in 3 of which there were maternal complications: the first, a fatal pulmonary infarction, the second, a puerperal pelvic infection, the third, an antepartum thigh abscess and a postpartum iliofemoral thrombosis. Six normal term infants were delivered.

The principal problem encountered was antepartum edema which subsided after delivery.

In terms of blood urea determinations and concentration tests, no evidence of impairment of renal function was observed.

RANDALL BLOOMFIELD

McFarlane and Truelove: Addison's Disease in Pregnancy, p. 891.

The authors report a case of hypoglycemic coma in pregnancy. The patient was at 30 weeks' gestation.

Pitocin induction of labor was performed with the subsequent delivery of a 2 pound, 7 ounce infant who died on the fifth day.

The pertinent postmortem findings were prematurity, thinning of the adrenal cortex, poor lung expansion, and perforation of the terminal ileum with peritonitis.

The diagnosis of adrenal cortical insufficiency was made post partum, and the patient showed a favorable response to cortisone therapy.

The essential features of the etiology, diagnosis, and management of Addison's disease are reviewed.

RANDALL BLOOMFIELD

Fertility and Sterility

Vol. 8, November–December, 1957.

*Rock, J.: Surgery for Female Infertility, p. 513.

Rock: Surgery for Female Infertility, p. 513.

In a rather brief essay the author voices his opinions of certain abnormalities for which surgery is often done. Interestingly enough, endometriosis occurred in approximately 30 per cent of his operative cases, although in only one half of these did the lesion appear to interfere with adnexal function. In other words, in approximately 15 per cent of operative cases the author found endometriosis of sufficient extent to account for the infertility of the patient. He points out the great value of culdoscopic examination in the recognition of both endometriosis and peritubal adhesions. In a discussion of tubal factors, mention is made of adhesions within the fimbria itself, allowing both gas and aqueous contrast medium to escape into the abdominal cavity. The author emphasizes the fact that it is only by laparotomy that discovery of such intrafimbrial adhesions is possible. In reference to tubal plastic surgery, he indicates the need for gentleness and sharp dissection, and advocates excision of the isthmus for implantation, and the use of polyethylene tubing and a perifimbrial polyethylene hood.

PAUL T. TOPKINS

Vol. 9, January–February, 1958.

*Clewe, T. H., and Mastroianni, L., Jr.: Mechanism of Ovum Pickup: I. Functional Capacity of Rabbit Oviducts Ligated Near the Fimbria, p. 13.

*Kupperman, H. S., Epstein, J. A., Blatt, M. H. G., and Stone, A.: The Diagnostic and Therapeutic Use of Intravenous Estrogen in Anovulation, p. 26.

*Potter, R. G., Jr.: Artificial Insemination by Donors: Analysis of Seven Series, p. 37.

*Horne, Herbert W., Jr.: Anencephaly in Four Consecutive Pregnancies: Report of a Case, p. 67.

Clewe and Mastroianni: Mechanism of Ovum Pickup: I. Functional Capacity of Rabbit Oviducts Ligated Near the Fimbria, p. 13.

In 11 immature rabbits the oviduct on one side was ligated at, or within 5 mm. of, the base of the fimbria, while the opposite oviduct served as a control. Seven to 14 days after placement of the ligature, ovulation was induced by a series of 3 daily subcutaneous injections of pregnant mare serum, followed in 12 hours by intravenous administration of equine pituitary gonadotropic substance. The animals were sacrificed 12 to 14 hours after the final ovulating injection, that is, 2 to 4 hours after the expected time of ovulation. The adnexa were removed and examined immediately in saline with a dissecting microscope. Ova were flushed from the control side with saline. On the experimental side the cul-de-sac formed by the ligature was opened by an incision from the edge of the fimbria to the ligature and the contents removed. After treatment with hyaluronidase to disperse the cumulus cells, the ova from each side were counted and the number of ova recovered was compared with the number of ovulation points on the associated ovary. One hundred per cent of the ovulated ova were recovered in 8 of the 11 ligated tubes and in 9 of the unligated tubes, indicating that a peristalsis-induced suction mechanism is not essential for ovum pickup in the rabbit. In addition, the results demonstrated that the function of the fimbria is sufficient to insure pickup of the ova without the aid of a strong fluid current through the tubal ostium.

PAUL T. TOPKINS

Kupperman et al.: Diagnostic and Therapeutic Use of Intravenous Estrogen in Anovulation, p. 26.

The authors used estrogens in anovulatory patients whose thyroid and adrenal cortical function was normal and whose endometrium showed adequate proliferative phase activity. A 20 mg. dose of conjugated equine estrogens was administered intravenously to a group of 31 patients with ovulatory failure. The injection was given 14 or more days after the onset of either a spontaneous menstrual period or one induced by progesterone. An ovulatory response was achieved in 16 patients. In this group there were 13 patients with a history of infertility averaging 4.3 years. Six of these became pregnant following the use of intravenous estrogen. The authors believe that if two successive doses of 20 mg. of conjugated estrogens, given at intervals of 2 weeks or more, are not followed by ovulation, the patient must be considered as having ovaries with follicle cysts and a thickened tunica, even without evidence of enlargement. Such patients should be subjected to wedge resection of the ovaries.

PAUL T. TOPKINS

Potter: Artificial Insemination by Donors: Analysis of Seven Series, p. 37.

The author carefully reviewed and analyzed 7 large series of cases of donor insemination published in this country in order to find out the relationship between the reported pregnancy rate and the procedure utilized by the investigator. Although many facts came to light, he realized very quickly that it was an extremely difficult task to make comparisons among the various reported series because of their lack of uniformity and thoroughness. He noted that each series showed some deficiencies and at the same time

certain compensatory aspects. Therefore, the author proposes that any report concerning donor insemination should have certain basic items of information, such as the number of months of insemination preceding each pregnancy or dropout of the patient, proper description of investigative procedures which establish a patient's fertility, description of the number of inseminations in each cycle and, when they are given, description of the technique and site of semen deposit, mention of the average age of the semen specimens at the time of use, together with how they were handled before being delivered, and the duration of the so-called "cooling off" periods between the first office visit and the first insemination. In addition, he suggests a description of any special provisions for emotional tension, as well as supplementary information such as the ages of the patients and the incidence of miscarriage.

PAUL T. TOPKINS

Horne: Anencephaly in Four Consecutive Pregnancies: Report of a Case, p. 67.

The author presents the case history of a patient who gave birth to anencephalic babies in 4 successive pregnancies. The first 3 pregnancies were the result of natural insemination by the patient's husband. The fourth pregnancy resulted from donor insemination, during the period of which the patient's husband used contraceptive precautions. The author points out that this very interesting case definitely places the onus on the maternal side as a genetic factor rather than an environmental one attributable to intrauterine influences.

PAUL T. TOPKINS

Revista Mexicana de Cirugía, Ginecología y Cáncer

Vol. 25, January, 1957.

*Morales, J. M., and Cabrera, J. F.: The Uterine Myoma and Its Relation to Sterility, p. 7.

Morales and Cabrera: The Uterine Myoma and Its Relation to Sterility, p. 7.

The authors reviewed 7,500 cases and found the incidence of uterine myomas to be 6.7 per cent (504 cases). Of these women with myomas, 27.2 per cent had a history of sterility, and, if women over 45 years and single women are eliminated, then the incidence of sterility in women with uterine myomas is raised to 42.36 per cent. Seventy-one and four-tenths per cent of the women had had no pregnancy in the 8 years preceding the diagnosis of myomas. The incidence of abortion is no higher than normal, however. The authors point out, therefore, that, while women with myomas have a higher incidence of sterility than normal women, perhaps this sterility is due to other concurrent diseases, such as inflammatory lesions, endometrial hyperplasia, etc. On the other hand, if a woman with myomas becomes pregnant, then she is no more likely to abort than a woman without myoma.

FRANCIS B. O'BRIEN

Science

Vol. 126, September, 1957.

*Arias, I. M., and London, I. M.: Bilirubin Glucuronide Formation in Vitro; Demonstration of a Defect in Gilbert's Disease, p. 563.

Arias and London: Bilirubin Glucuronide Formation in Vitro; Demonstration of a Defect in Gilbert's Disease, p. 563.

Incubation of bilirubin with liver extract, in phosphate buffer at pH 7.4 with magnesium chloride, ascorbic acid, and albumin, leads to the formation of direct-acting bilirubin. Hydrolysis of direct-acting bilirubin with acid or beta glucuronidase gives

indirect-acting bilirubin with the release of 1 mol of glucuronic acid for each mol of direct-acting bilirubin converted to the indirect-acting azo pigment. Liver extracts or isolated microsomes of patients with congenital hepatic dysfunction (Gilbert's disease) are markedly deficient in promoting the conjugation of bilirubin with glucuronic acid, to give direct-acting bilirubin.

The formation of direct-acting bilirubin in the liver involves an enzyme (transferase) found in the microsomes. This enzyme transfers glucuronic acid from uridin-diphosphate-glucuronic acid to bilirubin.

L. C. CHESLEY

Vol. 127, February, 1958.

*Woolley, D. W., and Edelman, P. M.: Displacement of Serotonin From Tissues by a Specific Antimetabolite, p. 281.

Woolley and Edelman: Displacement of Serotonin From Tissues by a Specific Antimetabolite, p. 281.

One-benzyl-2-methyl-5 methoxytryptamine (BAS) is a potent and highly specific antimetabolite of serotonin and might, therefore, be expected to displace serotonin from tissues. This expectation was confirmed in the following experiment: Platelets were isolated from the blood specimens of individual rabbits and the serotonin content found to average 2.7 μg per 10^8 platelets (16.1 μg per milligram of platelet protein). Measurements in whole, hemolyzed blood averaged 9.4 μg per milliliter of blood. The rabbits were then given 15 mg. per kilogram of BAS intraperitoneally for 3 days and blood was taken for analysis. The serotonin content was decreased by nearly half.

Repeated measurements in untreated control rabbits showed little variation from day to day. The effect of BAS was slow in onset (none at one hour after the first injection). Analysis by a chemical method checked closely with the pharmacologic assay.

It is suggested that reserpine may exert some of its pharmacologic effects by virtue of its antiserotonin property.

LEON C. CHESLEY

The Western Journal of Surgery, Obstetrics and Gynecology

Vol. 65, 1957.

*Morton, D. G., Moore, J. G., and Chong, N.: Endometrial Lavage as an Aid in the Diagnosis of the Endometrium, p. 113.

Morton, Moore, and Chong: Endometrial Lavage an an Aid in the Diagnosis of the Endometrium, p. 113.

The authors present a method for screening patients for possible carcinoma of the endometrium. They inject saline through a cannula in the cervical os, and allow the fluid to run back into the posterior fornix, where it is sucked up and deposited in a centrifuge tube, then stained. In 673 patients, endometrial carcinoma was diagnosed by this method in 24 of 26 histologically proved cases. Eleven false suspicious or false positive cases were noted.

ROBERT C. KNAPP

Correspondence

Further Light on Diagnosis of Brenner Tumor

To the Editors:

In July, 1957, we reported a case of an unusually large Brenner tumor (Am. J. Obst. & Gynec. **74**: 207, 1957). Since then I have received correspondence from two sources suggesting that this may be a metastatic ovarian tumor similar to that described by Krukenberg or that this may be an adenofibroma. Because of this doubt I requested reconsideration of this case by the Registry of Ovarian Tumors of the American Gynecological Society.

With Dr. J. Donald Woodruff's kind permission, I quote from his letter of Jan. 7, 1958:

"The impressions of Dr. Novak and of Dr. Ronald Greene express my opinion most completely. Dr. Novak, as you know, felt that this was a Brenner tumor, and Dr. Greene felt that it was an adenofibroma with metaplasia. Since there is little doubt at the present time that Brenner tumors arise as a metaplastic process from some pre-existing adenomatous formation, I feel that either one of these opinions would be quite acceptable, and would be essentially the same."

Inasmuch as this case did not turn out to be as clear-cut as one might desire, I feel that this information should be brought to the attention of the readers of this JOURNAL.

LOUIS H. AVERBACH, M.D.

FRANKFORD HOSPITAL
FRANKFORD AVENUE AND WAKELING STREET
PHILADELPHIA 24, PENNSYLVANIA
FEB. 27, 1958.

Items

The Society for the Scientific Study of Sex

This society will hold its first annual meeting on Nov. 8, 1958, at the Barbizon Plaza Hotel, New York City. For details write to Robert V. Sherwin, 1 East 42 Street, New York 17, New York.

Inter-Society Cytology Council

The Annual Scientific Meeting of the Inter-Society Cytology Council will be held at the Hotel Statler, New York, New York, Nov. 13, 14, and 15, 1958.

The Secretary is Paul F. Fletcher, M.D., 634 North Grand Avenue, St. Louis 3, Mo.

Union professionnelle internationale des gynécologues et obstetriciens

The Congress of the Union professionnelle internationale des gynécologues et obstetriciens will be held in Brussels, Belgium, on July 18 and 19, 1958.

For further information regarding the Congress, apply to Dr. Geeraert, 311, Avenue Louise, Brussels, Belgium.

Third World Congress on Fertility and Sterility

The Third World Congress on Fertility and Sterility, sponsored by the International Fertility Association, will be held in Amsterdam, Holland, from June 7-13, 1959.

The general outline of the sections of the program will be:

1. Female sterility
2. Male sterility
3. Basic research and/or animal reproduction
4. Psycho-sexual problems

Official languages: English, French, German, Spanish (with simultaneous translation).

Registration fee: full member $40 (U. S.), accompanying family-members $15 (U. S.). After Jan. 1, 1959, the registration for full members will be $50 (U. S.).

For further information and registration apply to Dr. L. I. Swaab, Hon. Secretary, Third World Congress on Fertility and Sterility, Sint Agnietenstraat 4, Amsterdam-C.

American Journal of

OBSTETRICS AND GYNECOLOGY

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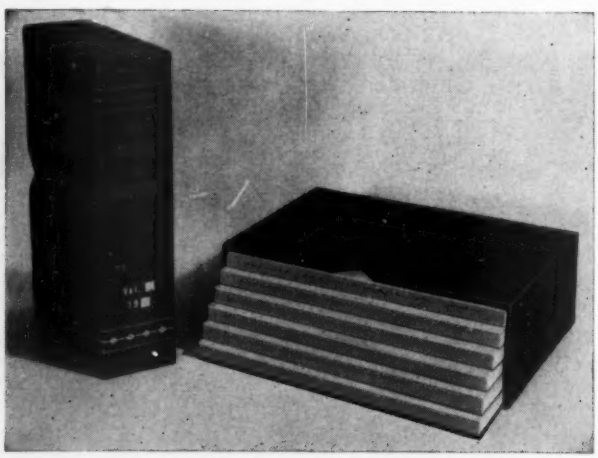

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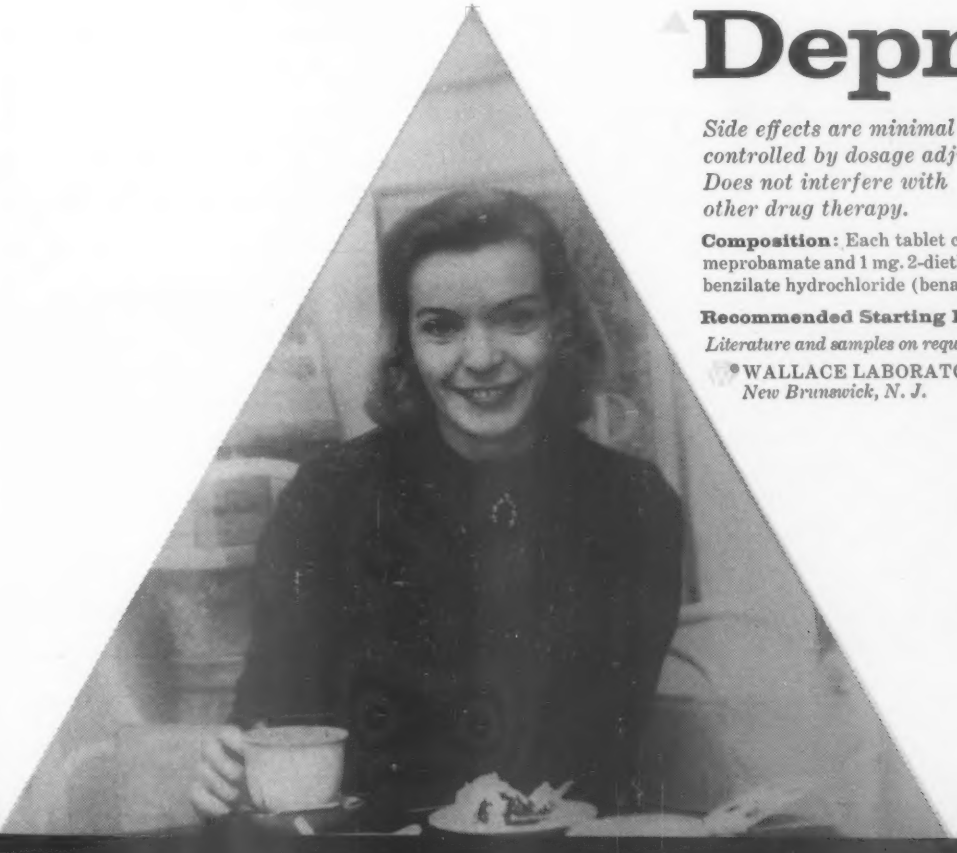

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Wilkins, R. W.: New England J. Med. **257**:1026, Nov. 21, 1957.

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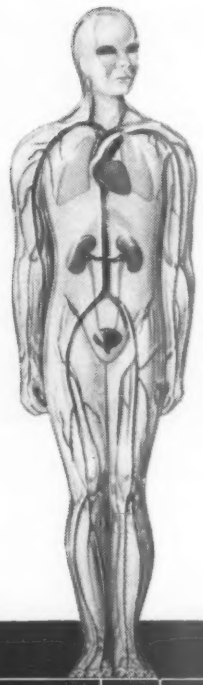

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. **166**:137, Jan. 11, 1958.

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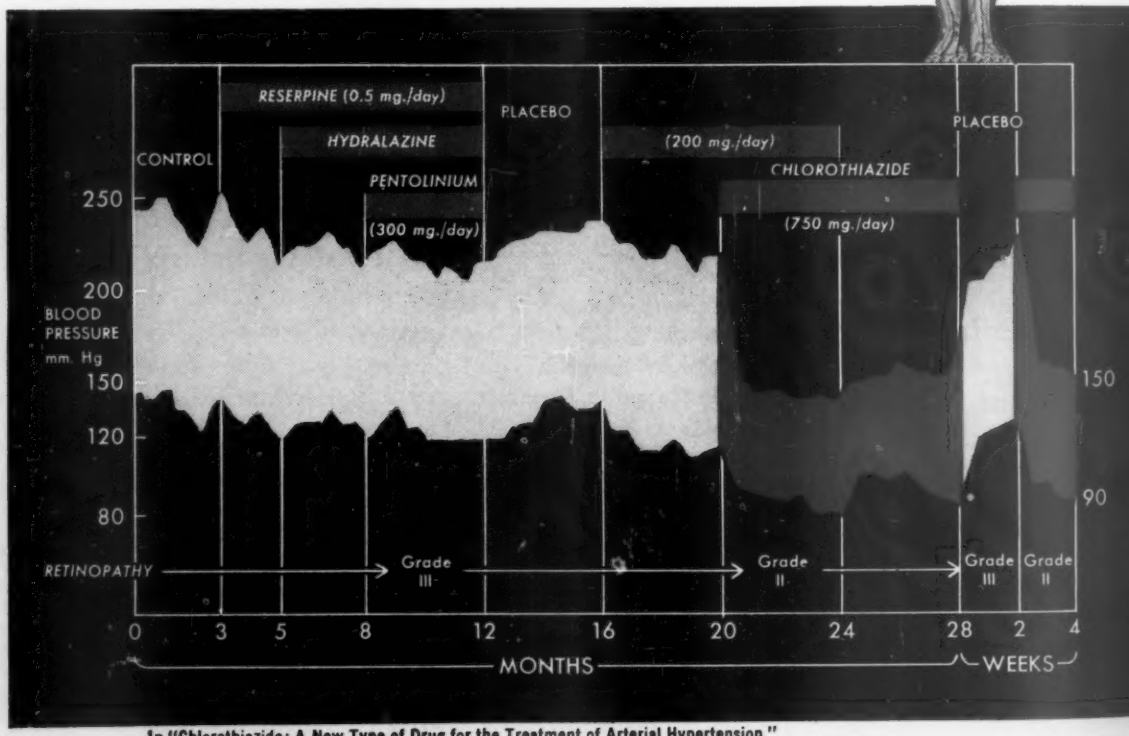

In "Chlorothiazide: A New Type of Drug for the Treatment of Arterial Hypertension," Hollander, W. and Wilkins, R. W.: Boston Med. Quart. **8**: 1, September, 1957.

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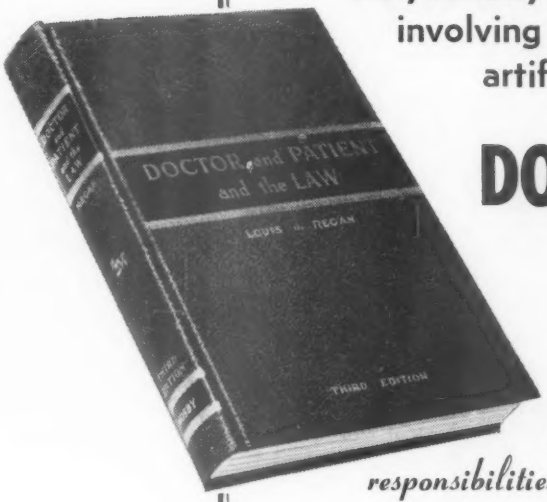

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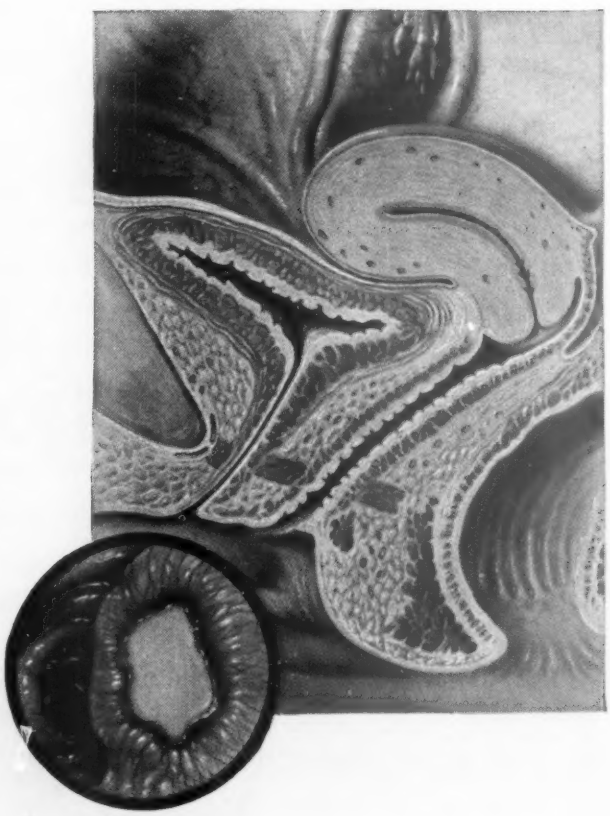

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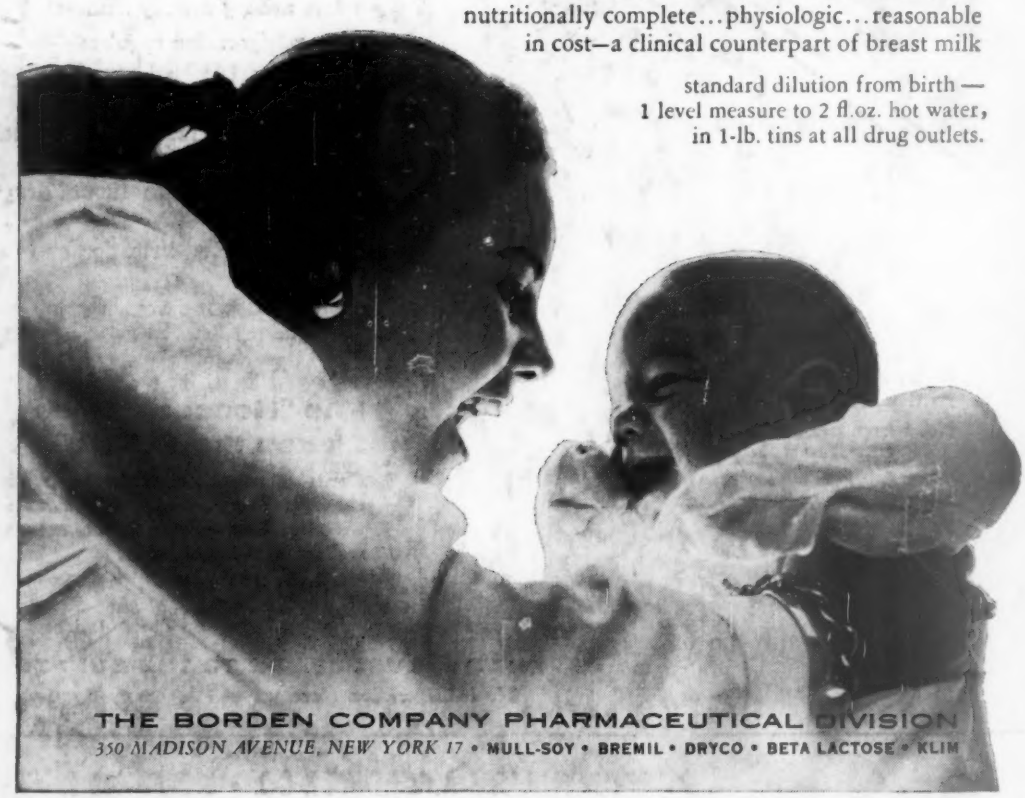
1 level measure to 2 fl.oz. hot water,
in 1-lb. tins at all drug outlets.



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